

2006

Synthesis of natural products in Hypericum and Echinacea

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Synthesis of natural products in *Hypericum* and *Echinacea*

by

Jingqiang Wei

A dissertation submitted to the graduate faculty
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

Program of Study Committee:

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Ames, Iowa

2006

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For the Major Program

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GENERAL INTRODUCTION

Plants, as a huge source of medicinal agents, have played a very important role in human history. As modern medicine developed, not only many useful drugs were discovered from medicinal plants, but also many botanical supplements have benefited human health. The synthesis of biologically active natural products and their analogs has become an important tool in drug discovery and life sciences.

Hypericum (St. John's wort) and *Echinacea* are two of the herbs most commonly used by consumers in the United States. As part of an NIH-funded Iowa Botanical Supplements Research Center, our group mainly focuses on the synthesis of active constituents in *Hypericum* and *Echinacea*.

In this context, we explore direct routes to the synthesis of several classes of natural products and analogs. During the process, novel synthetic methodologies are developed. The strategies we design will be useful to synthesize other structure-related natural products.

Thesis organization

In this thesis, the total synthesis of natural products in *Hypericum* (St. John's wort) and *Echinacea* as well as their analogs have been investigated. During the process, novel synthetic methodologies have been developed. This thesis is divided into five chapters.

Chapter 1 describes the direct synthesis of hyperolactone C in two steps using tandem Claisen rearrangement and lactonization as the key transformations.

Chapter 2 describes regioselective Diels-Alder reactions directed by remote substituents. This selectivity has useful application in natural products synthesis. The selectivity is explained by molecular electrostatic potential (MEP) calculations.

Chapter 3 describes the synthesis of the phytochemical medicinal reagents, pterocarpins, based on benzofuran and quinone coupling. In this synthesis, quinone monoketal replacement of the quinone moiety has extended the reaction scope.

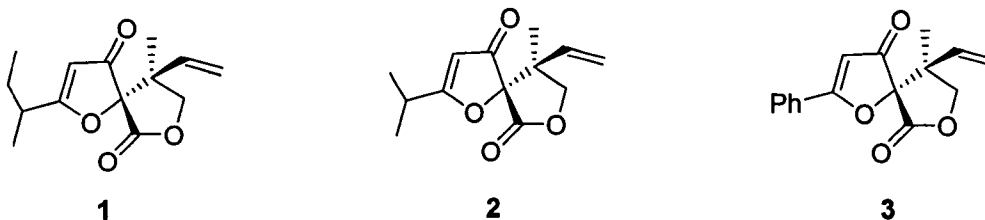
Chapter 4 describes a general synthesis of three classes of natural products: flavones, aurones, and acyl phloroglucinols from one type of intermediate 1,3-benzodioxin-4-ones. The regiochemistry of flavones has also been investigated to synthesize flavopyridol analogs.

Chapter 5 describes the total synthesis of lycorines. Oxogalathine lactam has been achieved by an oxidation of intramolecular Diels-Alder adducts. The intermediate could be applied to the total synthesis of lycorine and other lycorine-type alkaloids.

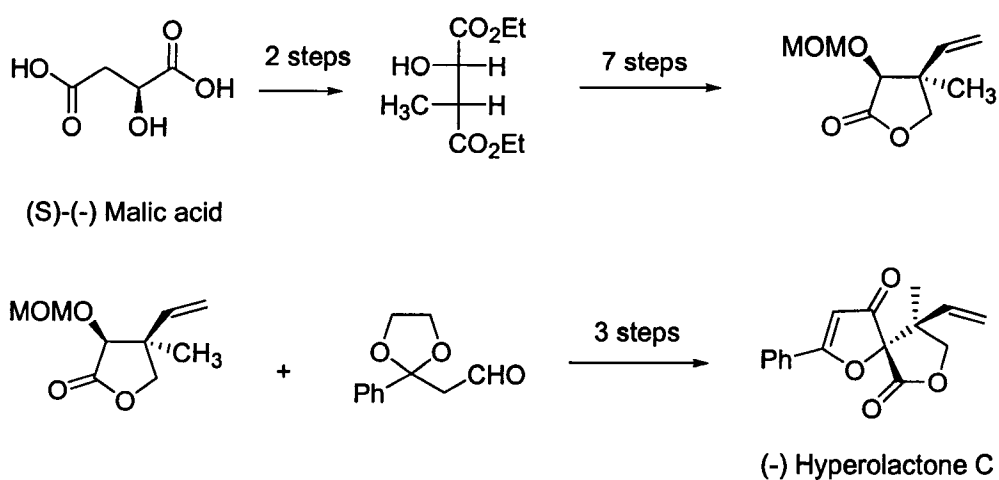
CHAPTER 1. DIRECT SYNTHESIS OF HYPEROLACTONE C

Introduction

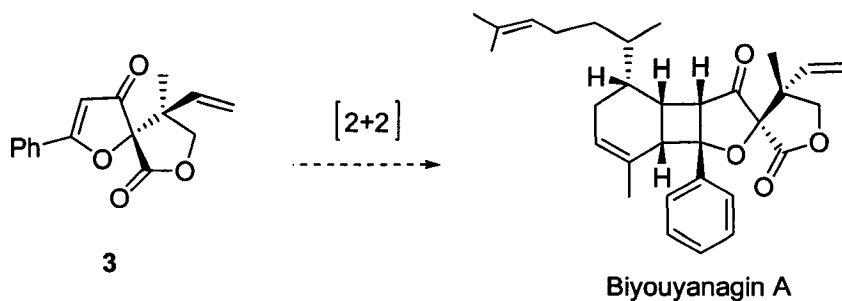
The hyperolactones constitute a growing class of novel metabolites isolated from *Hypericum chinense* L.¹ The structures of hyperolactone A (1), B (2), and C (3) are depicted below. In the context of a study of the metabolites of *Hypericum* through bioassay-guided fractions, an authentic sample of hyperolactone C was required. The extended conjugation (via the phenyl substituent) and resemblance to known antiviral agents made hyperolactone C a metabolite of interest.



Kinoshita and co-workers have reported interesting syntheses of hyperolactone A, B, and C from chiral precursors.^{2,3} The synthesis of hyperolactone C shown in the following scheme used (S)-(-) malic acid as the starting material. Although their synthesis defined the absolute stereochemistry in this series, sixteen steps were required to achieve the target. Therefore, a more direct synthetic approach is needed to support biological studies.

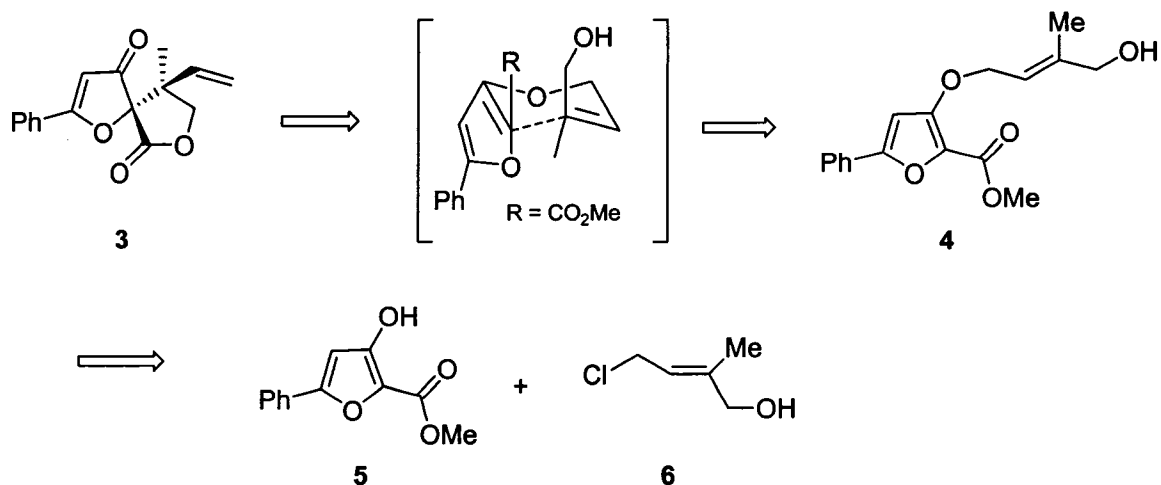


In 2005, a new natural product, biyouyanagin A, isolated from the same plant, *Hypericum chinense L.*, was reported as an anti-HIV agent.⁴ Its biosynthesis was proposed from hyperolactone C by a [2 + 2] cyclization. An efficient synthesis of hyperolactone C could provide starting materials to test this proposal.

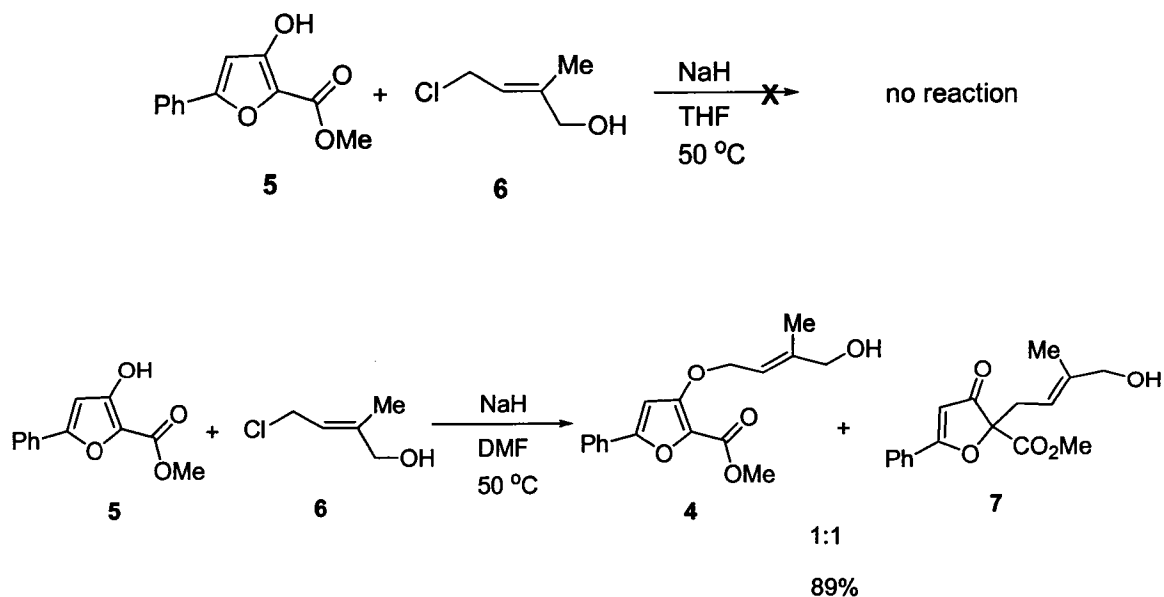


Results and Discussion

Hyperolactone C is expected to be synthesized by a tandem Claisen rearrangement-lactonization protocol.⁵ The retrosynthetic analysis is shown below. Such a protocol had not been reported, and it represented a novel strategy for constructing two adjacent quaternary centers.

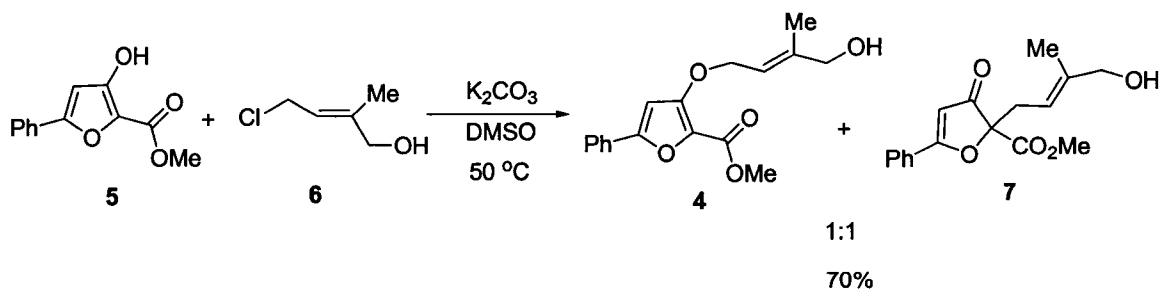
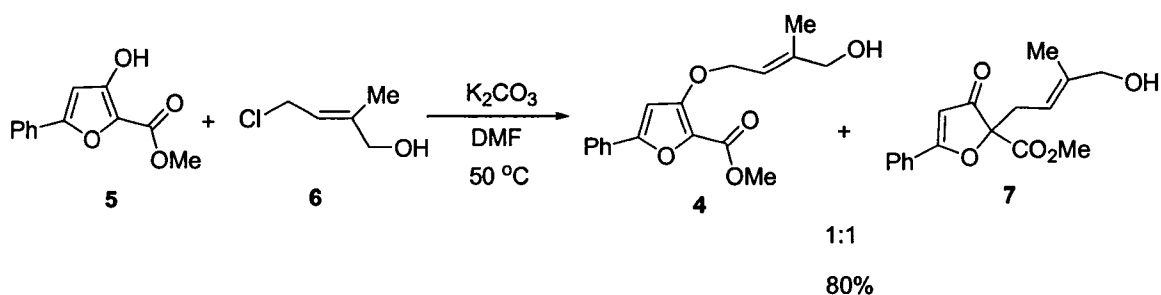


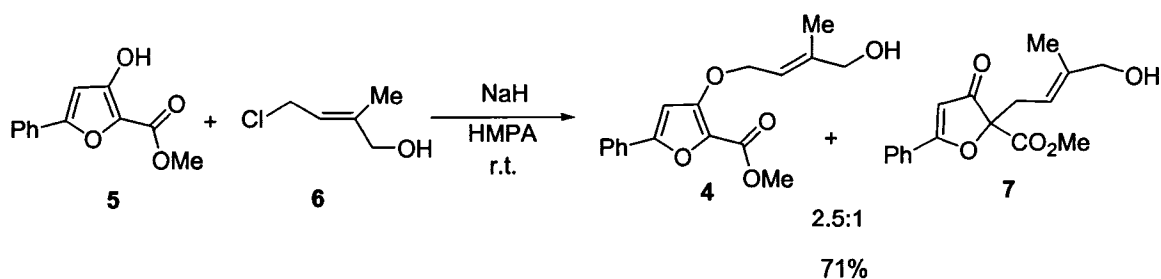
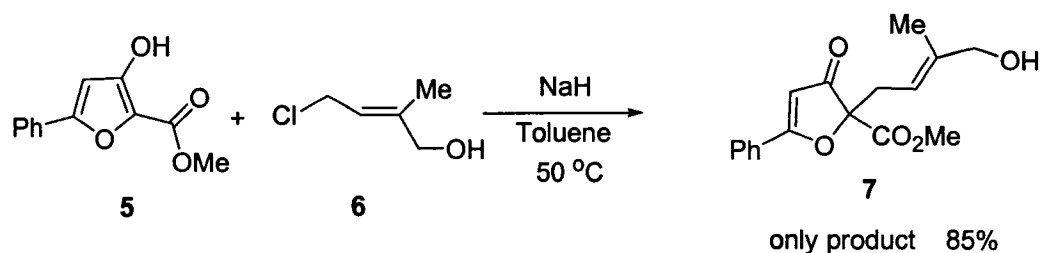
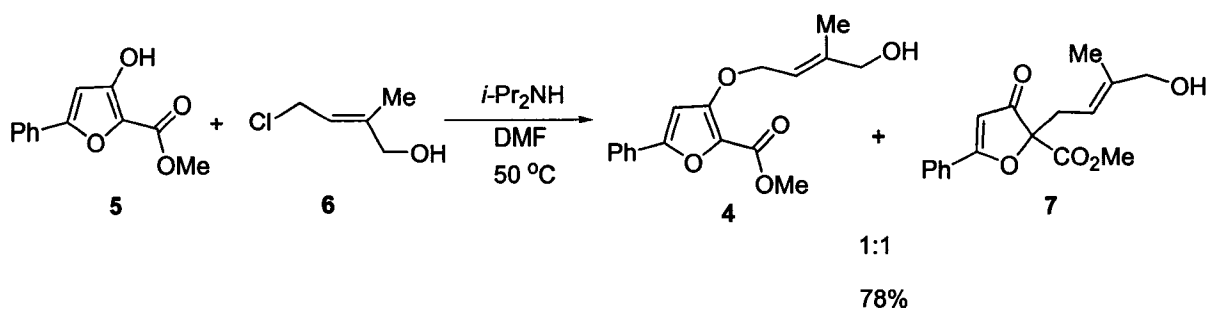
The synthesis started with the *O*-alkylation of furanol **5**, which was prepared from methyl acetoacetate,⁶ and allyl chloride **6**.⁷ The *O*-alkylation proved to be very solvent dependent. With THF as the solvent and NaH as the base, there was no reaction even when the mixture was heated to 50 °C.



In polar solvents, such as, DMF, and DMSO, we tried different bases, such as NaH, K_2CO_3 , and $i\text{-Pr}_2\text{NH}$. All these reactions gave both the *O*-alkylation product **4** and the *C*-alkylation product **7** in a 1:1 ratio.

When the non-polar solvent toluene was employed with NaH as the base, only the unexpected *C*-alkylation product **7** was isolated after the reaction. Fortunately, alkylation in HMPA at room temperature afforded a 2.5:1 ratio in favor of the desired product. The structure of **4** was supported by the methylene doublet at 4.77 ppm and the furan resonance at 6.60 ppm in the ^1H NMR spectrum.

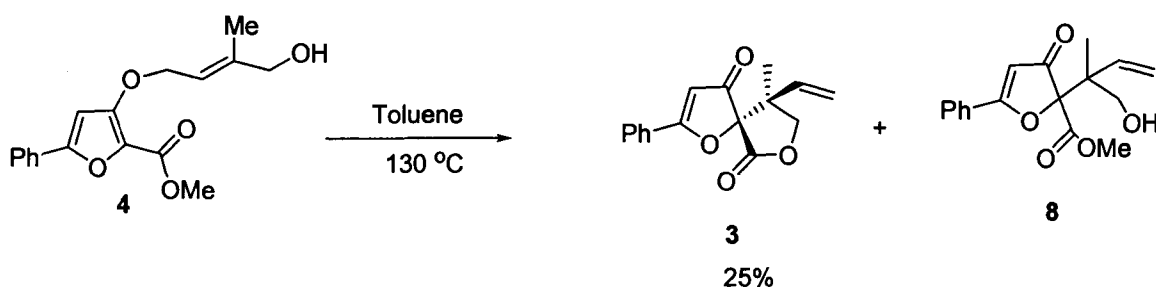




Although separable for analytical characterization, the mixture of 4 and 7 was heated in toluene at $130\text{ }^\circ\text{C}$ to provide 3 in 25% yield.

The ^1H NMR spectrum of 3 showed a methyl singlet at 1.53 ppm, resonances characteristic of a vinyl group attached to a quaternary carbon (doublets at 5.26 and 5.27 ppm plus a doublet of doublets at 5.99 ppm), and a singlet at 5.98 ppm for the enone hydrogen. The ^{13}C NMR showed 14 peaks, including a ketone resonance at 196.8 ppm and a lactone

resonance at 187.5 ppm. The ^1H and ^{13}C NMR spectra of our synthetic sample were identical to those reported for the natural product.^{1,3} The byproduct of the reaction, hydroxy ester **8**, was a mixture of diastereomers. It could not be converted into a lactone using heat, acid (PTSA), or base (*t*-BuOK, NaH, or KH) catalysis. Although the yield of **3** is modest, the synthetic route is convenient and amenable to the production of quantities of hyperolactone C for biological activity.



In conclusion, hyperolactone C is prepared from furanol **5** and allyl chloride **6** in two steps. The key step is a tandem Claisen rearrangement and lactonization.

Experimental Section

Unless stated otherwise, reactions were performed in flame-dried glassware under an argon atmosphere, using freshly distilled solvents. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methylene chloride (CH_2Cl_2), benzene, toluene and diisopropylamine (*i*-Pr₂NH) were distilled from calcium hydride. *N,N*-Dimethyl formamide (DMF), methyl sulfoxide (DMSO), and hexamethylphosphoramide (HMPA) were distilled from calcium hydride and stored over activated 4 Å molecular sieves in sealed containers.

Unless stated otherwise, all reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) plates, purchased from Aldrich (Cat. No. Z122785-25EA). Column or flash chromatography (silica) was performed with the indicated solvents using standard grade silica gel (particle size 230-400 mesh, 60 Å).

^1H and ^{13}C NMR spectra were obtained on either a Varian 300 MHz or a Bruker 400 MHz spectrometer. Chemical shifts are reported relative to internal Me_4Si (^1H and ^{13}C , δ 0.00 ppm) or chloroform (^1H , δ 7.26 ppm; ^{13}C , δ 77.0 ppm). All melting points were obtained on a MEL-TEMP II variable temperature melting point apparatus from Laboratory Devices and are uncorrected. High-resolution mass spectra were recorded on a Kratos model MS-50 spectrometer, and low-resolution mass spectra were recorded on a Finnegan 4023 mass spectrometer.

Preparation of 4 and 7

Procedure A: To methyl 2,3-dihydro-3-oxo-5-phenylfuran-2-carboxylate (**5**) (0.10 g, 0.46 mmol) in 4 mL of DMF at room temperature was added 60% NaH in mineral oil (19 mg, 0.48 mmol). After 1 h, (*E*)-4-chloro-2-methylbut-2-en-1-ol (**6**) (60 mg, 0.5 mmol) in 4 mL of DMF was added slowly at room temperature. The mixture was heated to 50 °C and stirred overnight. After the mixture was cooled to room temperature, 0.5M AcOH was added to quench the reaction, followed by 20 mL of H_2O . The solution was extracted with ethyl acetate (20 mL \times 2), washed with brine, and dried over Na_2SO_4 . Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 2:1) afforded *O*-alkylation product **4** and *C*-alkylation product **7** as a mixture (0.123 g, 89% yield) in a 1:1 ratio.

Procedure B: To methyl 2,3-dihydro-3-oxo-5-phenylfuran-2-carboxylate (**5**) (0.10 g, 0.46 mmol) in 4 mL of DMF at room temperature was added K_2CO_3 (0.13 g, 0.92 mmol). After 1 h, (*E*)-4-chloro-2-methylbut-2-en-1-ol (**6**) (60 mg, 0.5 mmol) in 4 mL of DMF was added slowly at room temperature. The mixture was heated to 50 °C and stirred overnight. After the mixture was cooled to room temperature, 0.5M AcOH was added to quench the reaction, followed by 20 mL of H_2O . The solution was extracted with ethyl acetate (20 mL \times 2), washed with brine, and dried over Na_2SO_4 . Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 2:1) afforded *O*-alkylation product **4** and *C*-alkylation product **7** as a mixture (0.111 g, 80% yield) in a 1:1 ratio.

Procedure C: To methyl 2,3-dihydro-3-oxo-5-phenylfuran-2-carboxylate (**5**) (0.10 g, 0.46 mmol) in 4 mL of DMSO at room temperature was added K_2CO_3 (0.13 g, 0.92 mmol). After 1 h, (*E*)-4-chloro-2-methylbut-2-en-1-ol (**6**) (60 mg, 0.5 mmol) in 4 mL of DMSO was added slowly at room temperature. The mixture was heated to 50 °C and stirred overnight. After the mixture was cooled to room temperature, 0.5M AcOH was added to quench the reaction, followed by 20 mL of H_2O . The solution was extracted with ethyl acetate (20 mL \times 2), washed with brine, and dried with Na_2SO_4 . Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate= 2:1) afforded *O*-alkylation product **4** and *C*-alkylation product **7** as a mixture (97 mg, 70% yield) in a 1:1 ratio.

Procedure D: To methyl 2,3-dihydro-3-oxo-5-phenylfuran-2-carboxylate (**5**) (0.10 g, 0.46 mmol) in 4 mL of DMF at room temperature was added diisopropylamine (93 mg, 0.92 mmol). After 1 h, (*E*)-4-Chloro-2-methylbut-2-en-1-ol (**6**) (60 mg, 0.5 mmol) in 4 mL of DMF was added slowly at room temperature. The mixture was heated to 50 °C and stirred overnight. After the mixture was cooled to room temperature, 0.5M AcOH was added to

quench the reaction, followed by 20 mL of H₂O. The solution was extracted with ethyl acetate (20 mL × 2), washed with brine, and dried over Na₂SO₄. Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 2:1) afforded *O*-alkylation product **4** and *C*-alkylation product **7** as a mixture (0.107 g, 78% yield) in a 1:1 ratio.

Procedure E: To methyl 2,3-dihydro-3-oxo-5-phenylfuran-2-carboxylate (**5**) (0.10 g, 0.46 mmol) in 4 mL of toluene at room temperature was added 60% NaH in mineral oil (19 mg, 0.48 mmol). After 1 h, (*E*)-4-chloro-2-methylbut-2-en-1-ol (**6**) (60 mg, 0.5 mmol) solution in 4 mL of toluene was added slowly at room temperature. The mixture was heated to 50 °C and stirred overnight. After the mixture was cooled to room temperature, 0.5M AcOH was added to quench the reaction, followed by 20 mL of H₂O. The solution was extracted with ethyl acetate (20 mL × 2), washed with brine, and dried over Na₂SO₄. Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 2:1) afforded only *C*-alkylation product **7** (0.118 g, 85% yield).

Procedure F: To methyl 2,3-dihydro-3-oxo-5-phenylfuran-2-carboxylate (**5**) (0.19 g, 0.87 mmol) in 4 mL of HMPA at room temperature was added 60% NaH in mineral oil (35 mg, 0.88 mmol). After 1 h, (*E*)-4-chloro-2-methylbut-2-en-1-ol (**6**) (0.11 g, 0.9 mmol) solution in 4 mL of HMPA was added slowly at room temperature. The mixture was stirred at room temperature overnight. 0.5M AcOH was added to quench the reaction, followed by 20 mL of H₂O. The solution was extracted with ethyl acetate (20 mL × 2), washed with brine, and dried with Na₂SO₄. Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 2:1) afforded *O*-alkylation product **4** and *C*-alkylation product **7** as a mixture (0.19 g, 71% yield) in a 2.5:1 ratio.

Compound 4: ^1H NMR (300 MHz, CDCl_3) δ 1.79 (s, 3H), 3.90 (s, 3H), 4.09 (s, 2H), 4.77 (d, $J = 6.3$ Hz, 2H), 5.78-5.83 (m, 1H), 6.60 (s, 1H), 7.33-7.45 (m, 3H), 7.73-7.77 (m, 2H); MS m/z 186, 218, 302; HRMS m/z for $\text{C}_{17}\text{H}_{18}\text{O}_5$ calcd. 302.1154, measd. 302.1159.

Compound 7: ^1H NMR (300 MHz, CDCl_3) δ 1.71 (s, 3H), 2.85-2.90 (m, 1H), 3.07-3.13 (m, 1H), 3.79 (s, 3H), 3.96 (s, 2H), 5.38-5.42 (m, 1H), 6.01 (s, 1H), 7.49-7.53 (m, 2H), 7.58-7.62 (m, 1H), 7.85-7.87 (m, 2H); HRMS m/z for $\text{C}_{17}\text{H}_{18}\text{O}_5$ calcd. 302.1154, measd. 302.1159.

Hyperolactone C (3)

The *O*-alkylation and *C*-alkylation product mixture (0.13 g, 0.43 mmol) was dissolved in 5 mL of toluene and heated in a sealed tube to 130 °C for 15 h. Evaporation of the solvent and flash chromatography (hexane/ethyl acetate, 4:1) afforded hyperolactone C (21 mg, 25% based on *O*-alkylation product). ^1H NMR (300 MHz, CDCl_3) δ 1.53 (s, 3H), 4.11 (d, $J = 8.4$ Hz, 1H), 4.97 (d, $J = 8.4$ Hz, 1H), 5.26 (d, $J = 17.7$ Hz, 1H), 5.27 (d, $J = 10.8$ Hz, 1H), 5.98 (s, 1H), 5.99 (dd, $J = 17.7$ Hz, 10.8 Hz, 2H), 7.49-7.55 (m, 2H), 7.58-7.64 (m, 1H), 7.84-7.87 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3) δ 19.8, 49.1, 74.4, 93.3, 100.5, 119.3, 127.6, 127.9, 129.3, 133.8, 134.5, 168.3, 187.5, 196.8. MS m/z 102, 160, 187, 211, 225, 270; HRMS m/z for $\text{C}_{16}\text{H}_{14}\text{O}_4$ calcd. 270.0892, measd. 270.0892.

Compound 8: ^1H NMR (300 MHz, CDCl_3) δ 1.27 and 1.38 (s, 3H), 3.79 and 3.81 (s, 3H), 4.24-4.30 and 4.65-4.71 (m, 2H), 4.65 and 4.67 (s, 1H), 5.17-5.26 (m, 2H), 5.73-6.07 (m, 1H), 6.01 and 6.03 (s, 1H), 7.46-7.60 (m, 3H), 7.79-7.83 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3) δ 16.2, 17.3, 44.4, 44.8, 55.1, 55.2, 70.8, 71.6, 86.5, 86.9, 102.6, 102.7, 117.2, 117.5, 127.3, 127.3, 129.2, 133.0, 136.3, 136.6, 155.8, 155.9, 185.2, 185.4, 202.3, 202.4. MS m/z 303 ($\text{M} + 1$), 270, 243, 227, 213, 187, 160, 143, 105.

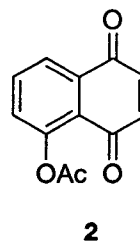
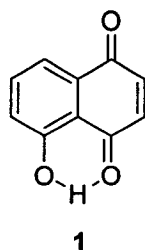
References

1. Aramaki, Y.; Chiba, K.; Tada, M. *Phytochemistry* **1995**, *38*, 1419-1421.
2. Ichinari, D.; Ueki, T.; Yoshihara, K.; Kinoshita, T. *Chem. Commun.* **1997**, 1743.
3. (a) Ueki, T.; Doe, M.; Tanaka, R.; Morimoto, Y.; Yoshihara, K.; Kinoshita, T. J. *Heterocycl. Chem.* **2001**, *38*, 165-172. (b) Ueki, T.; Ichinari, D.; Yoshihara, K.; Morimoto, Y.; Kinoshita, T. *Tetrahedron Lett.* **1998**, *39*, 667-668.
4. Tanaka, N.; Okasaka, M.; Ishimaru, Y.; Takaishi, Y.; Sato, M.; Okamoto, M.; Oshikawa, T.; Ahmed, S. U.; Consentino, L. M.; Lee, K. H. *Org. Lett.* **2005**, *7*, 2997-2999.
5. Tandem Claisen reactions: (a) Baskaran, S.; Nagy, E.; Braun, M. *Liebigs Ann./Recl.* **1997**, 311-312. (b) Newhouse, B. J.; Bordner, J.; Augeri, D. J.; Litts, C. S.; Kleinman, E. F. *J. Org. Chem.* **1992**, *57*, 6991-6995. (c) Kraus, G. A.; Woo, S. H. *J. Org. Chem.* **1987**, *52*, 4841-4846.
6. Yamamoto, M. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1688-1691.
7. Hecht, S.; Amslinger, S.; Jauch, J. *Tetrahedron Lett.* **2002**, *43*, 8929-8933.

CHAPTER 2. REGIOSELECTIVE DIELS-ALDER REACTIONS DIRECTED BY REMOTE SUBSTITUENTS

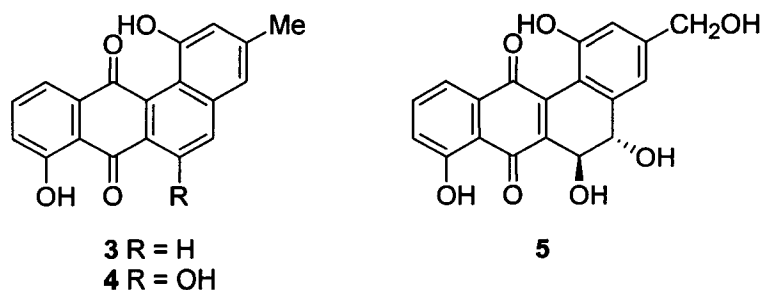
Introduction:

The Diels-Alder reaction has often been used to construct polycyclic quinines from either benzoquinones or naphthoquinones.¹ Generally, regioselective Diels-Alder reactions of quinone compounds require substituents directly attached to the quinone rings.² However, regioselective Diels-Alder reactions directed by remote substituents are seldom reported. The nature of oxygen's function in 5-hydroxy-1,4-naphthoquinone (**1**) and 5-acetoxy-1,4-naphthoquinone (**2**) profoundly influences the regiochemistry of the cycloaddition with 1-acetoxy-1,3-butadiene.³

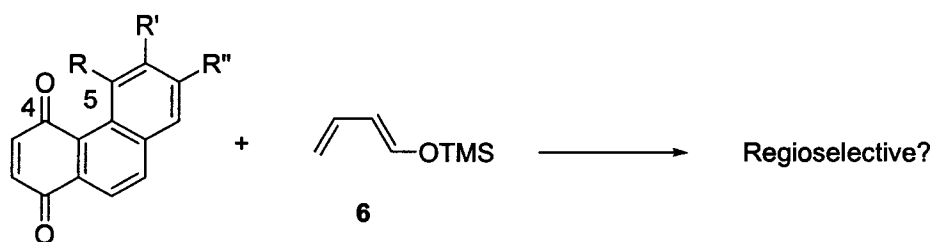


The rationale for this effect revolves around the concept that the strong hydrogen bond known to be present in quinone **1** serves as an “internal Lewis acid”, polarizing the unsaturated system, and results in the C-4 carbonyl serving as the dominant director of cycloaddition. Alternatively, electron donation by oxygen is considered to dominate in the acetate quinone **2**, leading to reversal of the regiochemical result.⁴

These regiochemically controlled reactions can be applied to the selective synthesis of angularly-fused ring systems. Natural products researchers have identified a number of tetracyclic and hexacyclic aromatic compounds that are angularly fused. Some of these compounds, such as tetrangulol (**3**), 6-hydroxytetrangulol (**4**), and PD116740 (**5**), exhibit significant biological activity.⁵ Recently, 6-hydroxytetrangulol was reported to be a CPP32 protease inducer.⁶ These compounds present significant challenges for the control of regiochemistry on carbons that are distant from one another, a challenge similar to that encountered in linearly fused anthracyclines. However, the presence of the angular fusion might confer opportunities for selectivity not available in linear systems. In our approach, the angularly fused ring system is regioselectively assembled by a strategy that takes advantage of the *proximity* of functional groups enforced by the angular fusion. This permits a strategy that is direct and significantly different from the previously reported approaches to these compounds.^{7,8}

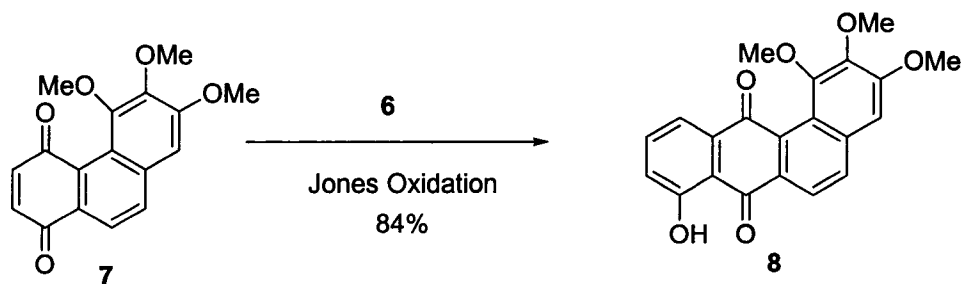


The key question in our approach to this system was whether the substituent at C-5 of a 1,4-phenanthrenequinone would, either by a steric or electronic effect, attenuate the directing effect of the carbonyl group at C-4.



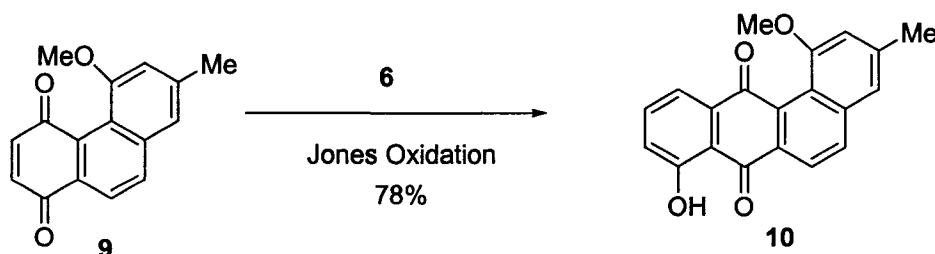
Results and Discussion

In order to test our hypothesis, quinone **7** was synthesized. The synthesis of **7** was accomplished using an intramolecular SnCl_4 -mediated cyclization of a hydroxy benzoquinone.⁹ The Diels-Alder adduct was produced by the addition of two equivalents of 1-(trimethylsilyloxy)-1,3-butadiene (**6**) to quinone **7** at -78°C , followed by warming to ambient temperature. The solvent was removed and the residue was oxidized using the Jones reagent.¹⁰ Product **8** was purified by silica gel flash column chromatography. No other quinone-containing products were detected. The regiochemistry of **8** was confirmed by an X-ray structure determination.¹¹ This result provides a novel approach to the problem of regiochemical communication in benzanthracene quinones.

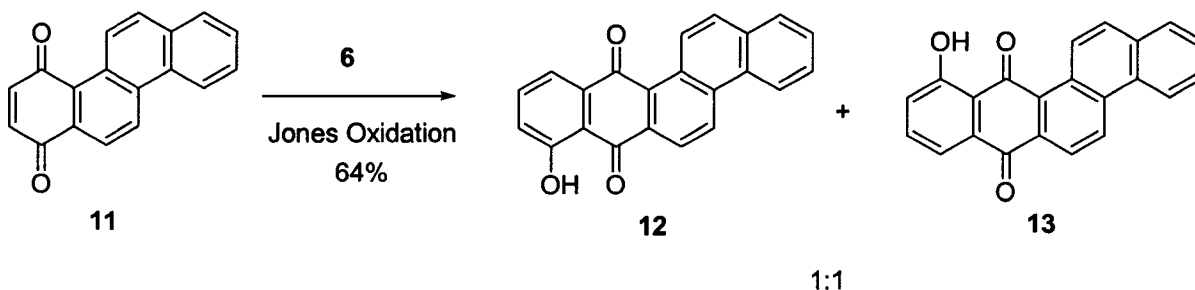


In order to better understand the scope of this interesting reaction, we decided to determine which substituents at C-5 would allow a regioselective Diels-Alder reaction.

Compound **9**¹² reacted with diene **6** at -78 °C in methylene chloride to produce quinone **10** in 78% isolated yield as the only isomer. The regiochemistry was confirmed by the transformation of **10** into tetrangulol **3** using iodotrimethylsilane.

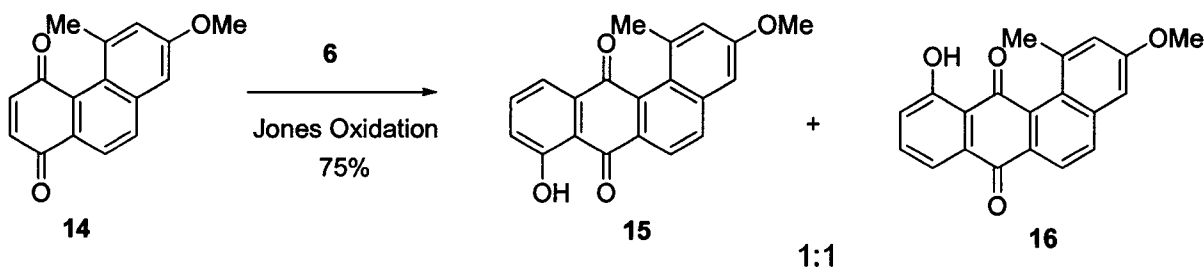


Commercially available chrysenequinone **11** was treated with diene **6**, followed by Jones oxidation. In this case, there is no substituent at C-5 to influence the carbonyl group at C-4. We were not surprised to isolate a 1:1 mixture of regioisomeric quinones **12** and **13** in a combined yield of 64%.

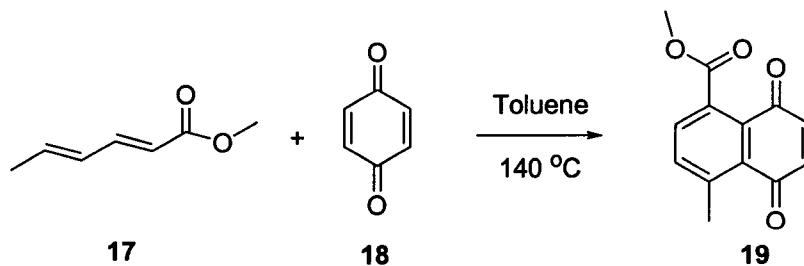


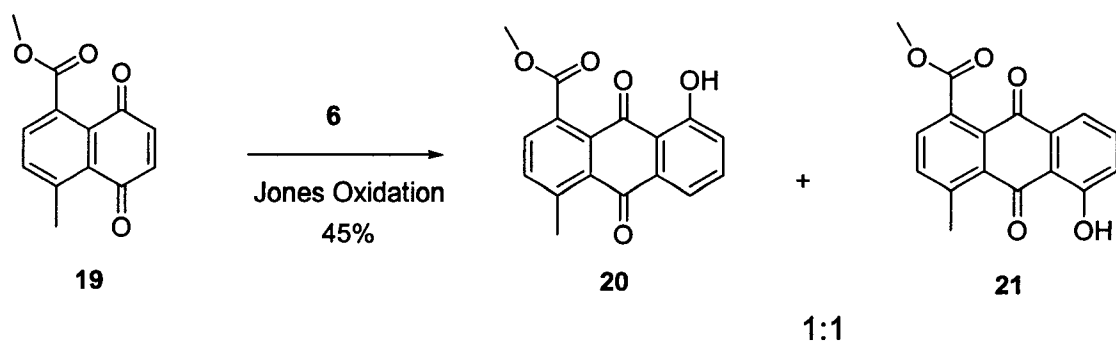
Quinone **14** was prepared from 3,5-dimethylanisole.^{12,13} The methyl group at C-5 allows us to assess the importance of steric attenuation of the carbonyl group at C-4. When treated with diene **6**, a 1:1 mixture of quinones **15** and **16** was produced. This result suggests

that the high regioselectivities observed with quinones **7** and **9** were primarily due to electronic interactions.

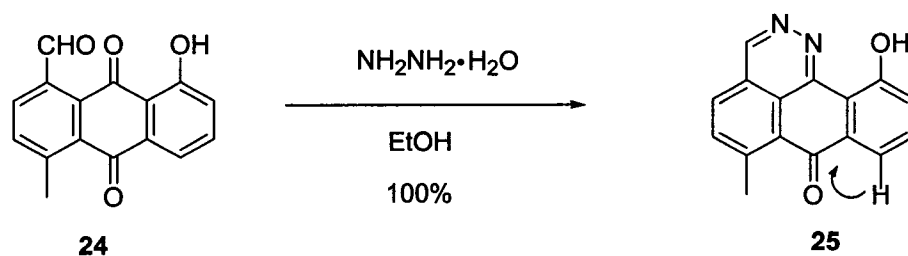
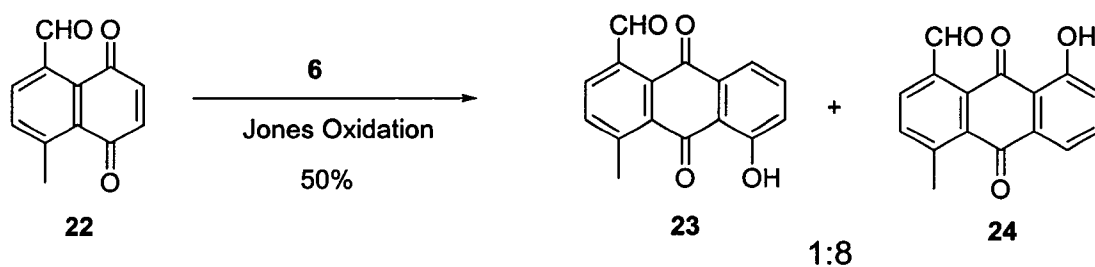


In order to expand the scope of this concerted reaction and further test the influence of remote functional groups on the regioselectivity, substituents have been introduced on the 5 position of 1,4-naphthoquinones to study the regioselectivities of the Diels-Alder reactions. Quinone **19** was synthesized by the Diels-Alder reaction of methyl sorbate (**17**) with excess 1,4-benzoquinone (**18**) in a sealed tube, using toluene as the solvent and heating to 140 °C. Quinone **19** reacts with diene **6**, followed by Jones oxidation, to give a 1:1 mixture of quinones **20** and **21** with no regioselectivity.

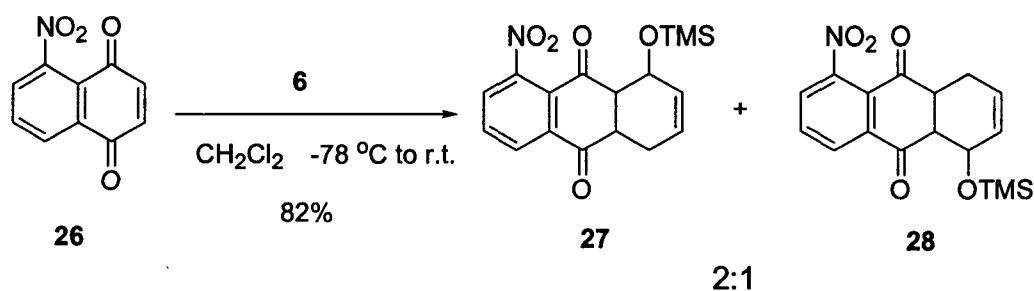




Quinone **22** was then synthesized by the reaction of 2,4-hexadienal with excess benzoquinone at 90 °C for 20 hours.¹⁴ It reacted with **6** to produce an 8:1 ratio of two anthraquinones. The major isomer was treated with hydrazine to produce compound **25** in quantitative yield. HMBC (Heteronuclear Multiple Bond Correlation) spectroscopy revealed a three-bond coupling between the carbonyl group and the hydrogen atom *peri*- to the carbonyl group, thereby defining the structure as **25** and the major isomer of the products of the reaction of **22** with **6** as anthraquinone **24**.



5-Nitro-1,4-naphthoquinone (**26**) was prepared by the nitration of 1,4-naphthoquinone.¹⁵ It reacts with diene **6** from -78 °C to room temperature to afford adducts **27** and **28** in a 2:1 ratio. Unfortunately, neither Jones reagent nor other oxidants could oxidize the mixture of adducts to the corresponding anthraquinones.



Theoretical Analysis

The geometry of **7** was fully optimized at the RHF/6-31G(d)¹⁶ level of theory and verified as a minimum by an analytical Hessian calculation, using the quantum chemistry program GAMESS.¹⁷ The calculated geometry shows that the quinone is significantly distorted from planarity (Figure 1b) to minimize the repulsive interaction with the C-5 methoxyl group. To gauge the effect of this distortion on the regioselectivity, molecular electrostatic potential (MEP) maps were evaluated 2Å above and below the dienophile (DP) plane.¹⁸ The terms "above" and "below" are defined in Figure 1.

Our calculations suggest that the regiocontrol is due to relatively long range electrostatic interactions between the substituents rather than through HOMO-LUMO interactions. We undertook these calculations precisely because the regiocontrol is not readily explainable in terms of traditional HOMO-LUMO arguments. The MEP maps (Figures 1a and 1c) show the molecular potential felt by a positive test charge and identify

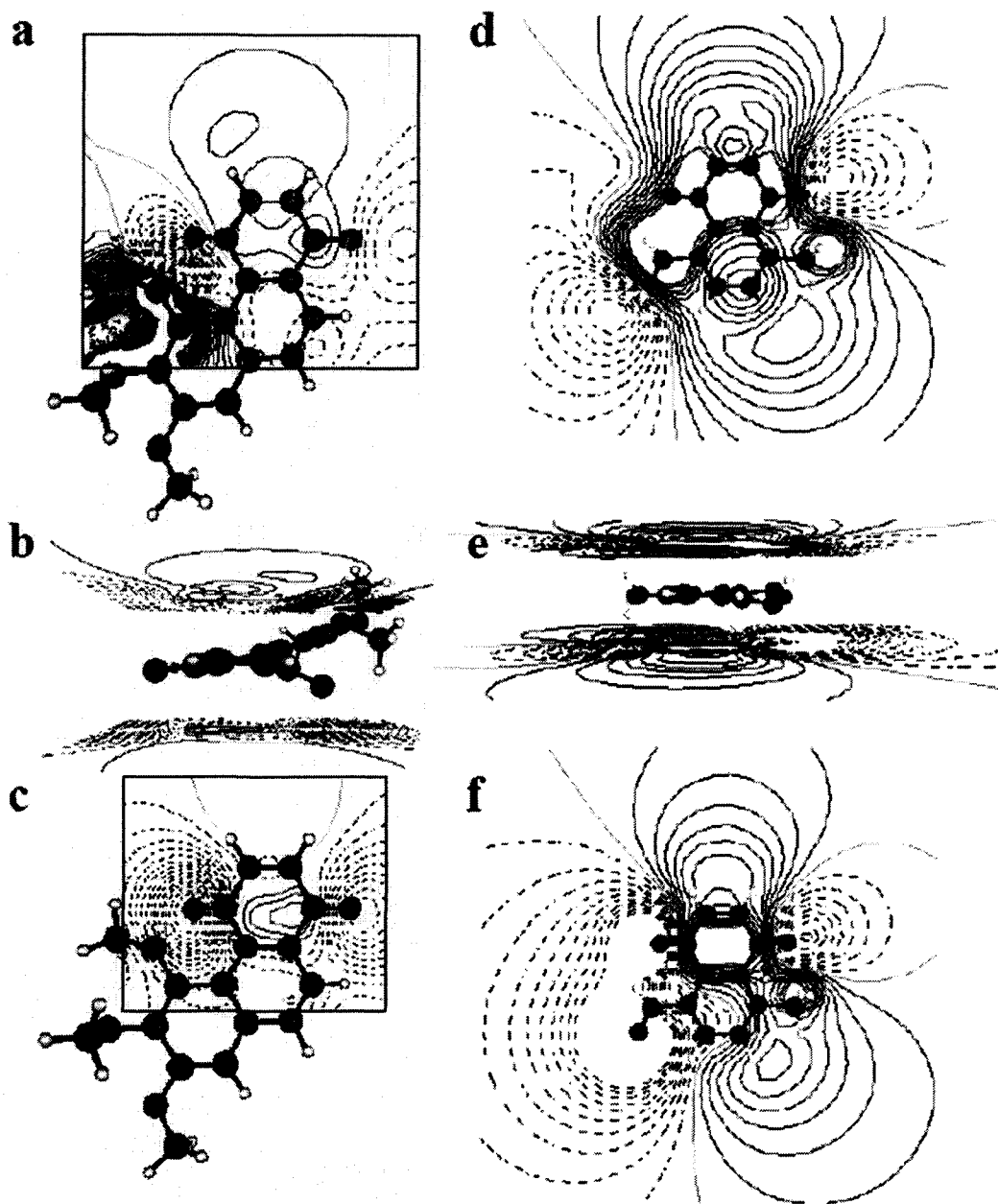


Figure 1. MEPs of **7** evaluated in planes 2 Å above (a) and below (c) the plane of the site of dienophile attack (defined in b), and similarly for **22** (d-f)

relative positive (solid contours) and negative parts (dotted contours) of the molecule. Both MEPs show a positive center region and negative regions at either side. The MEP 2 Å below the DP plane (Figure 1c) shows an almost equal negative charge distribution on either side due to the quinone oxygens. The MEP 2 Å above the DP plane (Figure 1a) shows more concentrated negative charge on the C-4 side of the ring due mostly to the C-5 methoxyl oxygen, and little negative charge on the C-1 side. Thus, these MEP maps indicate that an incoming 1-(trimethylsilyloxy)-1,3-butadiene should attack **4** from above with the OTMS group away from the C-5 methoxyl group. An MEP of 1-(trimethylsilyloxy)-1,3-butadiene has been published as Figure 2 in reference 6b. The reaction is not likely to modify the partial charges of the substituents controlling regioselectivity, because they are remote from the region that undergoes chemical change.

A similar analysis of the MEP of **15** also explains the observed selectivity. The aldehyde group is shown to distort the quinone group, though to a lesser extent than for **4** (compare Figures 1b and 1e). Thus, the aldehyde group and neighboring quinone oxygen protrude from opposite sides of the quinone ring. As a result, the least negative region of the dienophile, and hence the preferred location of the OTMS group upon attack is on the “aldehyde side” of the ring and adjacent to the aldehyde. Thus, compound **17** is predicted to be the preferred product in accord with our experimental findings.

Experimental Section

Unless stated otherwise, all reactions were performed in flame-dried glassware under a argon atmosphere, using freshly distilled solvents. Diethyl ether (Et₂O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methylene chloride

(CH₂Cl₂), benzene, toluene and diisopropylamine (*i*-Pr₂NH) were distilled from calcium hydride. *N,N*-Dimethyl formamide (DMF), methyl sulfoxide (DMSO), and hexamethylphosphoramide (HMPA) were distilled from calcium hydride and stored over activated 4 Å molecular sieves in sealed containers.

Unless stated otherwise, all reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) plates purchased from Aldrich (Cat. No. Z122785-25EA). Column or flash chromatography (silica) was performed with the indicated solvents using standard grade silica gel (particle size 230-400 mesh, 60 Å).

All ¹H and ¹³C NMR spectra were performed on either a Varian 300 MHz or a Bruker 400 MHz spectrometer. Chemical shifts are reported relative to internal Me₄Si (¹H and ¹³C, δ 0.00 ppm) or chloroform (¹H, δ 7.26 ppm; ¹³C, δ 77.0 ppm). All melting points were obtained on a MEL-TEMP II variable temperature melting point apparatus from Laboratory Devices and are uncorrected. High-resolution mass spectra were recorded on a Kratos model MS-50 spectrometer, and low-resolution mass spectra were recorded on a Finnegan 4023 mass spectrometer.

General Procedure for the Diels-Alder/Oxidation

To a solution of the 1,4-phenanthrenequinone (0.2 mmol) in dry CH₂Cl₂ (2 mL) was added dropwise 1-(trimethylsilyloxy)-1,3-butadiene (**5**) (0.07 mL, 0.4 mmol) at -78 °C under argon. The resulting solution was slowly warmed to room temperature and stirred overnight. After removal of solvent *in vacuo*, the residue was dissolved in acetone (5 mL) and was treated with 2.7 M Jones reagent (0.163 mL, 0.44 mmol) at 0 °C. The resulting red mixture was allowed to warm to room temperature and after 1 h was quenched with excess 2-

propanol. After stirring for an additional 5 min, the mixture was concentrated *in vacuo*. The residue was partitioned between CH₂Cl₂ and saturated NH₄Cl. The solvent was removed and the residue was purified by silica gel flash chromatography (sgc).

8-Hydroxy-1,2,3-trimethoxybenz[a]anthracene-7,12-dione (8)

Purified by sgc (4:1 hexane: ethyl acetate) to give **6** (61 mg, 84% yield) as a red solids: m.p. = 232 °C; ¹H NMR (300 MHz, CDCl₃) δ 3.98 (s, 1H), 4.03 (s, 6H), 6.99 (s, 1H), 7.23 (dd, *J* = 1.8, 7.2 Hz, 1H), 7.58-7.66 (m, 2H), 7.90 (d, *J* = 8.7 Hz, 1H), 8.16 (d, *J* = 8.7 Hz, 1H), 12.24 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 56.2, 61.1, 61.3, 102.9, 115.6, 118.2, 120.8, 121.5, 122.7, 131.8, 132.1, 135.2, 136.6, 136.7, 137.1, 143.9, 150.7, 156.2, 161.6, 185.9, 188.3; IR (KBr) 2945, 1681, 1632, 1600 cm⁻¹; HRMS *m/z* for C₂₁H₁₆O₆ calcd: 364.0947, measured: 364.0949.

8-Hydroxy-1-methoxy-3-methylbenz[a]anthracene-7,12-dione (10)

Purified by sgc (60:1 hexane: ethyl acetate) to give **10** (49.6 mg, 78% yield) as a red solid: m.p. = 211-212 °C; ¹H NMR (300 MHz, CDCl₃) δ 12.2 (s, 1H), 8.22-8.19 (d, 1H, *J* = 8.4 Hz), 7.96-7.93 (d, *J* = 8.4 Hz, 1H), 7.64-7.59 (m, 2H), 7.28 (s, 1H), 7.24-7.21 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.91 (s, 1H), 3.98 (s, 3H), 2.54 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 188.3, 185.5, 161.4, 157.3, 141.1, 138.4, 137.1, 137.1, 136.5, 132.6, 132.5, 122.5, 121.8, 120.0, 119.7, 118.2, 115.4, 111.4, 56.0, 22.2; IR (KBr) 1673, 1633 cm⁻¹; MS *m/z* 318 (M⁺, base peak), 301 (M-OH⁺) HRMS *m/z* for C₂₀H₁₄O₄ calc. 318.2559, measured: 318.2563.

8-Hydroxy-3-methoxy-1-methylbenz[a]anthracene-7,12-dione (15) and 11-hydroxy-3-methoxy-1-methylbenz[a]anthracene-7,12-dione (16)

Purified by sgc (hexane: ethyl acetate = 10:1) to give **15** and **16** as a dark brown liquid.

^1H NMR (300 MHz, CDCl_3) δ 2.50 and 2.54 (s, 3H), 3.95 and 3.97 (s, 3H), 6.99-7.80 (m, 4H), 7.95-8.07 (m, 2H), 8.23 and 8.25 (d, $J = 6.6$ Hz, 1H), 11.83 and 12.29 (s, 1H).

8-Hydroxybenzo[*b*]chrysene-7,12-dione (12) and 11-hydroxybenzo[*b*]chrysene-7,12-dione (13)

To 1,4-chrysenequinone (11) (0.05 g, 0.19 mmol) in 5 mL of CH_2Cl_2 at 0 °C, 1-(trimethylsilyloxy)-1,3-butadiene (0.28 g, 1.9 mmol) was added slowly. The solution was warmed up to room temperature slowly and stirred 2 days. Vacuum evaporation removed the solvent and the residue was dissolved in 5 mL of acetone. Jones reagent (8N, 1.2 mmol) was added dropwise at 0 °C. The mixture was warmed up to room temperature slowly and was stirred for 4 hours at room temperature. Vacuum evaporation removed the solvent. The residue was extracted with CH_2Cl_2 (20 mL \times 2) and saturated NH_4Cl (20 mL). The organic layers were combined, washed with brine, and dried with MgSO_4 . After vacuum evaporation, the residue was purified by silica gel chromatography (hexane: ethyl acetate = 4:1) and recrystallization with 1:1 hexane/ethyl acetate to give 12 and 13 (39 mg, 64% yield) as orange crystals in a 1:1 ratio. ^1H NMR (300 MHz, CDCl_3) δ 7.28-7.36 (m, 1H), 7.64-7.75 (m, 3H), 7.82-7.86 (m, 1H), 7.95-7.97 (m, 1H), 8.00-8.05 (m, 1H), 8.57-8.60 (m, 1H), 8.73-8.76 (m, 1H), 9.11-9.16 (m, 1H), 9.58 and 9.69 (d, $J = 9.9$ Hz, 1H), 12.45 and 12.87 (s, 1H). MS m/z 324, 277, 239, 201, 169, 120; HRMS m/z for $\text{C}_{22}\text{H}_{12}\text{O}_3$ calcd. 324.0786, measured 324.0793. TLC (hexane: ethyl acetate = 2:1) $R_f = 0.65$.

4-Methyl-5,8-dioxo-5,8-dihydronaphthalene-1-carboxylic acid methyl ester (19)

To a sealed tube, methyl sorbate (**17**) (0.252 g, 2 mmol) and 1,4-benzoquinone (**18**) (0.432 g, 4 mmol) were added, followed by 2 mL of toluene. The mixture was heated to 140 °C for 10 h, cooled to room temperature and a minimum amount of CH₂Cl₂ was added to transfer all the mixture on silica gel chromatography (hexane: ethyl acetate= 2:1) to give 1,4-naphthoquinone ester **19** (0.13 g, 28% yield). ¹H NMR (300 MHz, CDCl₃) δ 2.79 (s, 3H), 3.98 (s, 3H), 6.93 (s, 2H), 7.58 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 20.3, 53.2, 129.9, 130.9, 131.5, 132.9, 137.2, 137.5, 140.2, 143.3, 170.1, 184.6, 186.5. TLC (hexane: ethyl acetate = 2:1) R_f = 0.55.

8-Hydroxy-4-methyl-9,10-dioxo-9,10-dihydroanthracene-1-carboxylic acid methyl ester (20**) and 5-hydroxy-4-methyl-9,10-dioxo-9,10-dihydroanthracene-1-carboxylic acid methyl ester (**21**)**

To the naphthoquinone **19** (46 mg, 0.2 mmol) in CH₂Cl₂ (3 mL) at -78 °C, 1-(trimethylsilyloxy)-1,3-butadiene (0.2 mL, 1.1 mmol) was added dropwise. The mixture was stirred overnight and the temperature was increased slowly to room temperature. After the solvent was removed under vacuum, the residue was dissolved in 5 mL of acetone and cooled to 0 °C, then treated with 2.7M Jones reagent (0.37 mL, 1 mmol). After 10 minutes, the mixture was concentrated under vacuum. The residue was partitioned between 10 mL of CH₂Cl₂ and 10 mL of saturated NH₄Cl solution. The organic layer was washed with brine, dried by Na₂SO₄, purified by flash chromatography to give **20** and **21** (26 mg, 45% yield) in a 1:1 ratio as yellow solids. ¹H NMR (300 MHz, CDCl₃) δ 2.88 and 2.91 (s, 3H), 4.02 and 4.03 (s, 3H), 7.28-7.34 (m, 1H), 7.55-7.77 (m, 4H), 12.07 and 12.69 (s, -OH); MS *m/z* 296,

265, 236; HRMS m/z for $C_{17}H_{12}O_5$ calcd. 296.0685, measured 296.0690. TLC (hexane: ethyl acetate = 3:1) R_f = 0.60.

4-Methyl-5,8-dioxo-5,8-dihydro-naphthalene-1-carbaldehyde (22)

To a 50 mL round bottom flask were added 2,4-hexadienal (0.5 g, 0.5 mmol), 1,4-benzoquinone (2.1 g, 20 mmol), and toluene (6 mL). The mixture was stirred and heated to 90 °C for 20 h. The solvent was removed under reduced pressure. Flash chromatography (hexane: ethyl acetate, 10:1) afforded quinone **22** (0.14 g, 14% yield), and recovered 2,4-hexadienal (0.14 g, 28% yield). 1H NMR (300 MHz, $CDCl_3$) δ 2.83 (s, 3H), 6.99 (d, J = 0.9 Hz, 2H), 7.66 (d, J = 8.1 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 10.53 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5, 130.1, 132.5, 133.6, 137.3, 137.4, 138.2, 140.3, 146.3, 186.3, 187.0, 192.4; MS m/z 200, 115, 57; HRMS m/z for $C_{12}H_8O_3$ calculated 200.0473, measured 200.0476. TLC (hexane: ethyl acetate = 4:1) R_f = 0.30.

1-Formyl-5-hydroxy-4-methyl-9,10-anthraquinone (23) and 1-formyl-4-methyl-8-hydroxy-9,10-anthraquinone (24)

To the naphthoquinone **22** (40 mg, 0.2 mmol) in CH_2Cl_2 (3 mL) at -78 °C, 1-(trimethylsilyloxy)-1,3-butadiene (0.2 mL, 1.1 mmol) was added dropwise. The mixture was stirred overnight and the temperature was increased slowly to room temperature. After the solvent was removed under vacuum, the residue was dissolved in 5 mL of acetone and cooled to 0 °C, then treated with 2.7M Jones reagent (0.37 mL, 1 mmol). After 10 minutes, the mixture was concentrated under vacuum. The residue was partitioned between 10 mL of CH_2Cl_2 and 10 mL of saturated NH_4Cl solution. The organic layer was washed with brine,

dried by Na₂SO₄, and purified by flash chromatography (hexane: ethyl acetate, 10:1) to give **23** and **24** (26.6 mg, 50% yield) as orange solids in a 1:8 ratio.

1-Formyl-5-hydroxy-4-methyl-9,10-anthraquinone (23)

¹H NMR (300 MHz, CDCl₃) δ 2.95 (s, 3H), 7.32 (dd, J = 5.1, 1.5 Hz, 1H), 7.69–7.87 (m, 4H), 10.50 (s, 1H), 12.03 (s, 1 H); MS m/z 266, 237, 181, 152; HRMS m/z for C₁₆H₁₀O₄ calcd. 266.0579, measured 266.0583. TLC (hexane: ethyl acetate = 4:1) R_f = 0.40.

1-Formyl-8-hydroxy-4-methyl-9, 10-anthraquinone (24)

¹H NMR (300 MHz, CDCl₃) δ 2.91 (s, 3H), 7.32 (dd, J = 5.1, 1.5 Hz, 1H), 7.69–7.87 (m, 4H), 10.63 (s, 1H), 12.03 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 24.1, 115.6, 119.7, 123.9, 131.9, 132.6, 134.1, 134.3, 137.5, 138.5, 138.9, 146.6, 162.0, 183.8, 189.8, 192.4; MS m/z 266, 237, 181, 152; HRMS m/z for C₁₆H₁₀O₄ calcd. 266.0579, measured 266.0583. TLC (hexane: ethyl acetate = 4:1) R_f = 0.40.

11-Hydroxy-6-methyl-dibenzocinnolin-7-one (25)

Anthraquinone **24** (20 mg, 0.075 mmol) was dissolved in 10 mL of ethanol, followed by hydrazine monohydrate (3.8 mg, 0.075 mmol) addition. The mixture was refluxed at 82 °C for 4 hours until the reaction was complete as monitored by TLC. After the mixture was cooled to room temperature, the solvent was removed by vacuum evaporation. The residue was partitioned between 10 mL of CH₂Cl₂ and 10 mL of water. The organic layer was washed with brine, dried by Na₂SO₄, and purified by flash chromatography (hexane: ethyl acetate = 3:1) to give **25** (20 mg, 100% yield) as an orange solid. ¹H NMR (400 MHz, CDCl₃) δ 3.08 (s, 3H), 7.38 (d, J = 8.0 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.94 (m, 2 H), 8.13 (d, J = 8.4 Hz, 1H), 9.46 (s, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 24.9, 115.4, 119.7, 123.0,

123.5, 124.2, 125.0, 131.7, 133.1, 134.1, 138.9, 149.7, 151.5, 152.9, 160.0, 183.6; MS m/z 262, 234, 151; HRMS m/z for $C_{16}H_{10}N_2O_2$ calcd. 262.0742, measured 262.0747. TLC (hexane: ethyl acetate = 3:1) R_f = 0.25.

8-Nitro-1-trimethylsilanyloxy-1,4,4a,9a-tetrahydro-anthraquinone (27) and 5-nitro-1-trimethylsilyloxy-1,4,4a,9a-tetrahydroanthraquinone (28)

To a solution of 5-nitro-[1,4] naphthoquinone (**26**) (40 mg, 0.2 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise 1-(trimethylsilyloxy)-1,3-butadiene (**5**) (0.07 mL, 0.4 mmol) at -78 °C under argon. The resulting solution was allowed to slowly warm to room temperature overnight. The mixture was partitioned between 10 mL of CH_2Cl_2 and 10 mL of water. The organic layer was washed with brine, dried by Na_2SO_4 , and purified by flash chromatography (hexane: ethyl acetate = 3:1) to give **27** and **28** (56.6 mg, 82% yield) as a reddish solid. 1H NMR (300 MHz, $CDCl_3$) -0.30 and -0.28 (s, 9H), 2.13-2.21 (m, 1H), 3.07-3.09, 3.13-3.16, and 3.21- 3.23 (m, 1H), 3.31-3.40 (m) and 3.52 (t, J = 6.3 Hz, 1H), 4.39-4.44 (m, 1H), 5.75-5.81 (m, 1H), 5.89-5.93 (m, 1H), 7.60- 7.84 (m, 2H), 8.19 and 8.23 (dd, J = 4.8, 1.2 Hz, 1H); MS m/z 417, 330, 256, 152, 142, 127; HRMS m/z for $C_{17}H_{19}NO_5Si$ calcd. 345.1032, measured 345.1039. TLC (hexane: ethyl acetate = 3:1) R_f = 0.50.

References

1. Desmoni, G. "Natural Products Synthesis"; American Chemical Society: Washington, DC **1983**; ACS Monogr. No.180.
2. Kraus, G. A.; Woo, S. Y. *J. Org. Chem.* **1986**, *51*, 114-116.

3. (a) Inhoffen, H.; Muxfeldt, H.; Schaefer, H.; and Kramer, H. *Croat. Chem. Acta*. **1957**, *29*, 329-345. (b) Muxfeldt, H. *Angew. Chem.* **1962**, *74*, 825-828.
4. Boeckman, R. K.; Dolak, T. M.; Culos, K. O. *J. Am. Chem. Soc.* **1978**, *100*, 7098-7100.
5. (a) Rohr, J.; Thiericke, R. *Natural Product Reports* **1992**, *9*, 103-137. (b) Wilton, J. H.; Cheney, D. C.; Hokanson, G. C.; French, J. C.; He, C.; Clardy, J. *J. Org. Chem.* **1985**, *50*, 3936-3938.
6. Yamashita, N.; Harada, T.; Shin-Ya, K.; Seto, H. *J. Antibiot.* **1998**, *51*, 79-81.
7. (a) Parker, K. A.; Ding, Q.-J. *Tetrahedron* **2000**, *56*, 10249-10254. (b) Hauser, F. M.; Dorsch, W. A.; Mal, D. *Org. Lett.* **2002**, *4*, 2237-2239.
8. Synthesis of angucyclines: (a) Krohn, K.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 128-195. (b) Carreno, M. C.; Urbano, A. *Synlett*. **2005**, 1-25.
9. Kraus, G. A.; Melekhov, A. *J. Org. Chem.* **1999**, *64*, 1720-1722.
10. The Diels-Alder/Jones oxidation sequence has been employed previously in our regioselective synthesis of frenolicin B: (a) Kraus, G. A.; Li, J.; Gordon, M.; Jensen, J. *J. Am. Chem. Soc.* **1993**, *115*, 5859-5860. (b) Kraus, G. A.; Li, J.; Gordon, M.; Jensen, J. H. *J. Org. Chem.* **1995**, *60*, 1154-1159.
11. Guzei, I. A.; Melekhov, A.; Kraus, G. A. *Acta Cryst.* **1999**, *C55*, 620.
12. Kraus, G. A.; Zhang, N.; Melekhov, A.; Jensen, J. H. *Synlett* **2001**, 521-522.
13. Kraus, G. A.; Hoover, K.; Zhang, N. *Tetrahedron Lett.* **2002**, *43*, 5319-5321.
14. Mashraqui, S.; Keehn, P. *Synth. Commun.* **1982**, *12*, 637-645.
15. Bu, X.; Deady, L. W.; Finlay, G. J.; Baguley, B. C.; Denny, W. A. *J. Med. Chem.* **2001**, *44*, 2004-2014.

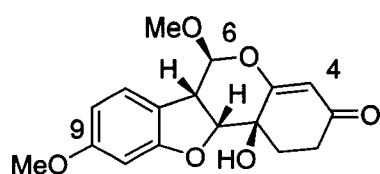
16. Harihanan, P. C.; Pople, J. A. *Theor. Chim. Acta.* **1973**, *28*, 213.
17. Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M.; Montgomery Jr., J. A. *J. Comp. Chem.* **1993**, *14*, 1347.
18. Bode, B. M. MacMolPlt
(<http://www.msg.ameslab.gov/GAMESS/Graphics/MacMolPlt.shtml>)

CHAPTER 3. SYNTHESIS OF PHYTOCHEMICAL MEDICINAL REAGENTS:

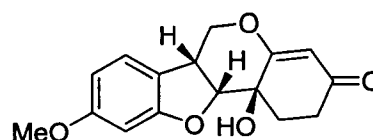
A QUINONE-BASED ROUTE TO PTEROCARPINS

Introduction:

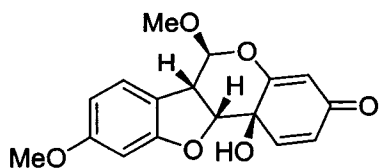
Kushecarpin A was recently isolated from *Sophora flavescens* by methanol extraction of the roots.¹ This novel pterocarpin exhibited significant antibacterial activities against the Gram-positive bacteria *Staphylococcus aureus*, *Bacillus subtilis*, *S. epidermidis*, and *Propionibacterium acnes*.¹ Related compound pterocarpan was isolated from the chloroform extract of *Ononius viscosa* subsp. *breviflora*,² and medicarpin was isolated from red clover (*Trifolium pretense* L.) and alfalfa (*Medicago sativa* L.)³ The anonymous benzofuran type pterocarpin has been reported to be a constituent of *Lespedeza* species.⁴ Despite their novel structures and potentially valuable biological activity, no synthetic approaches to pterocarpins have been reported.



Kushecarpin A



Pterocarpan



Medicarpin

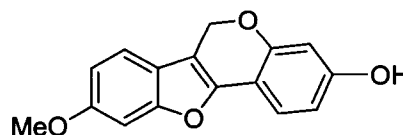
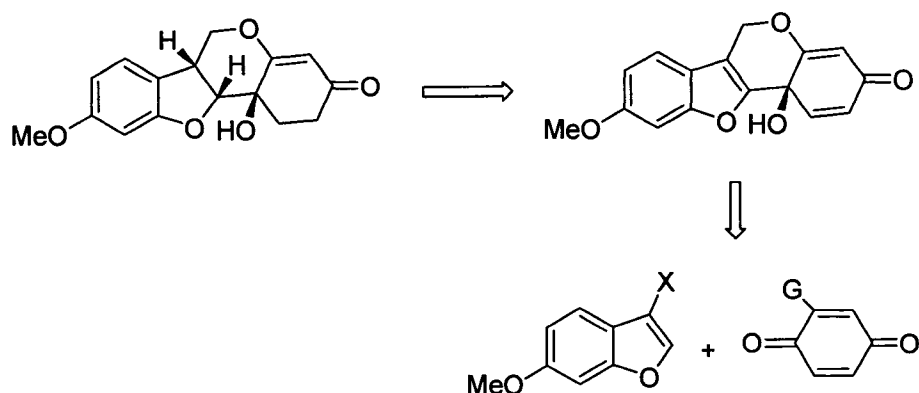


Figure 1. Structures of the named and anonymous phytochemical medical reagents.

Results and Discussion

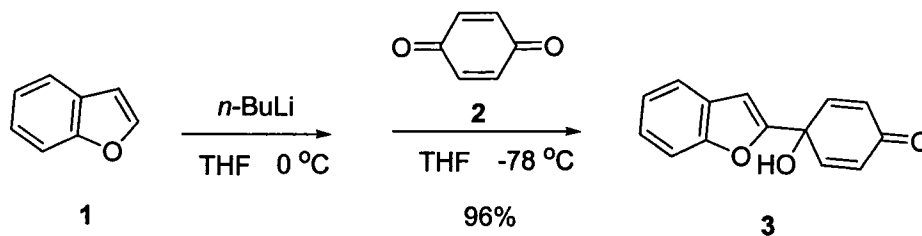
As part of a program to identify useful plant medicinal agents,⁵ we describe herein a convenient and direct preparation of pterocarpan featuring the addition of the anion of a benzofuran to a synthetic equivalent of methoxy-1,4-benzoquinone.



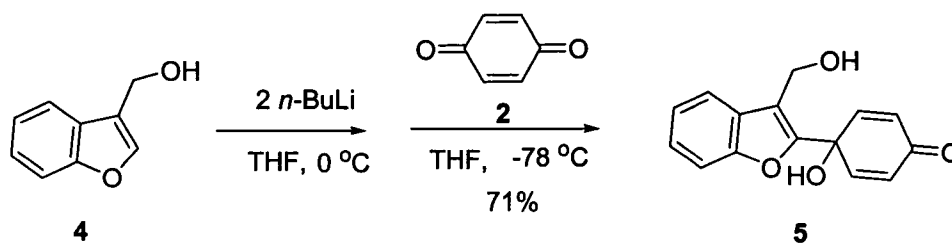
This strategy is based on the hydroxyl-directed stereoselective hydrogenation of a cyclohexadienone intermediate, which was viewed as a key intermediate, because hydroxyl-directed hydrogenation⁶ was expected to install the dihydrobenzofuran unit with the methine hydrogens on the same face of the molecule as the hydroxyl group. The cyclohexadienone intermediate in turn would be synthesized from a readily available 3-substituted benzofuran and 2-substituted 1,4-benzoquinone.⁷ If G represents an electron-donating substituent, the regioselective reaction of an organolithium reagent with the benzoquinone at the carbonyl required for the synthesis of the cyclohexadienone intermediate has good precedent.⁸

In order to test the benzofuran anion coupling with 1,4-benzoquinone, we started the synthesis with some model reactions. First, 2,3-benzofuran was treated with *n*-butyl lithium

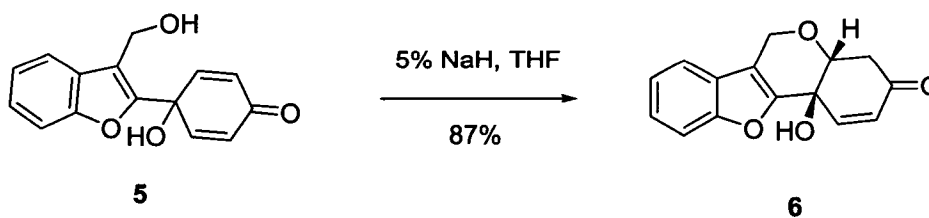
in THF at 0 °C for one hour, followed by the addition of 1,4-benzoquinone at -78 °C to give quinonol **3** in 96% yield.⁹



When 3-substituted benzofuran **4** was used, the dianion coupling with 1,4-benzoquinone (**2**) was also successful to give the desired hydroxycyclohexadienone **5**. The next step was to transform the benzofuran to a tetracyclic compound.



Compound **5** reacted readily under basic conditions to afford alcohol **6**. The most convenient conditions for scale up involved sodium hydride in THF at 25 °C.



With the tetracyclic system in hand, reduction of the benzofuran was examined. Surprisingly, alcohol **6** did not react using the iridium-based directed hydrogenation conditions. Catalytic hydrogenation using Pd/C afforded a single stereoisomer based on the proton and carbon NMR spectra. The structure of **7** was determined by X-ray crystallography (see Figure 2).¹⁰ Most Pd/C catalyzed hydrogenations are not stereoselective. Herein, the selectivity from **6** to **7** is due to the molecular geometry of **6**, which is bent and rigid. The top face of this molecule is the only face that allows Pd/C to approach to introduce the *cis* hydrogens relative to the hydroxyl group.

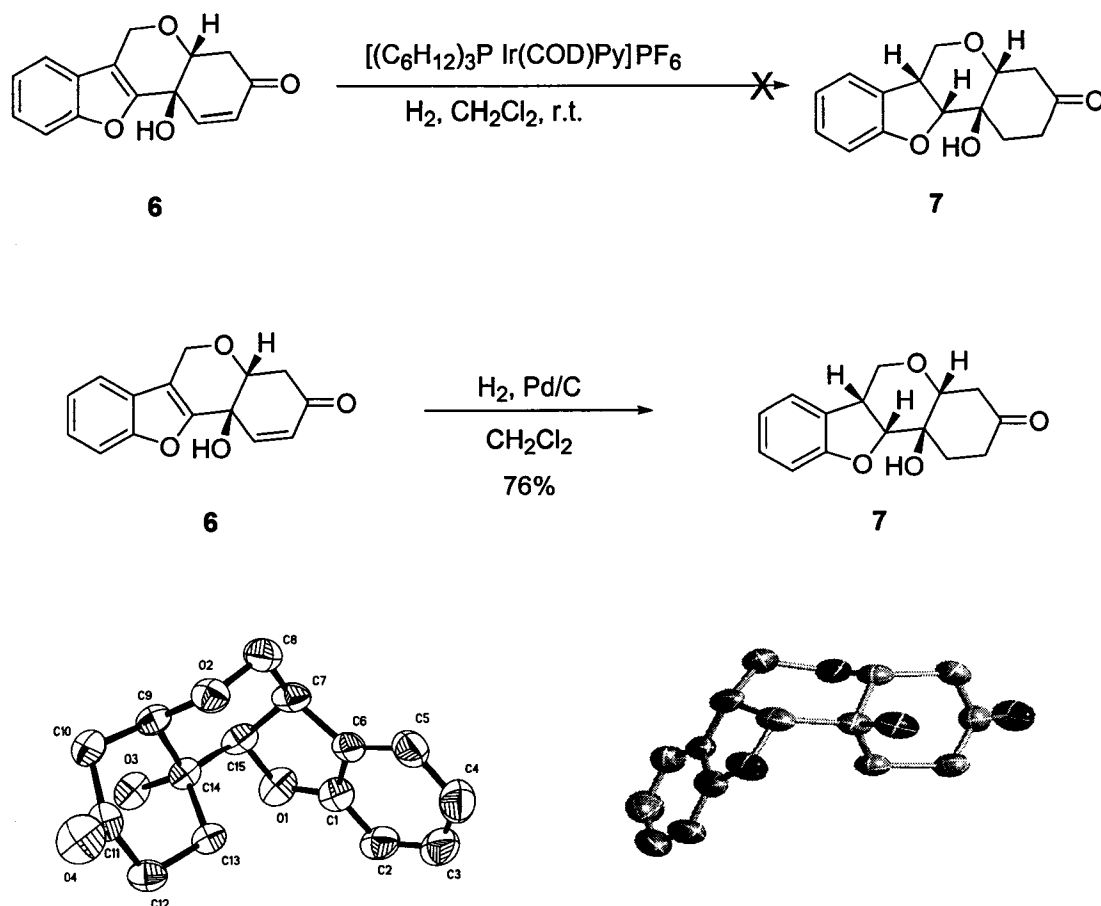
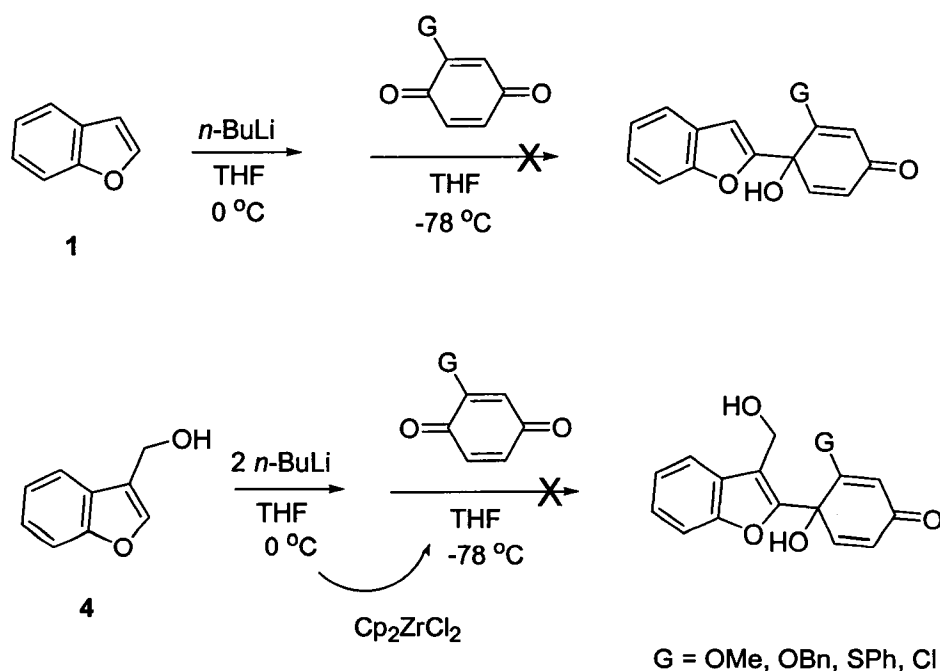
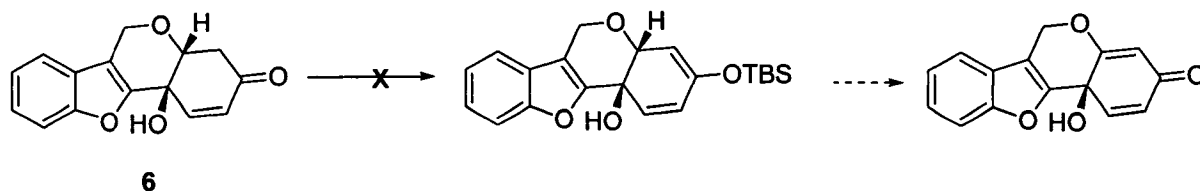


Figure 2. Single crystal X-ray structure of compound **7**.

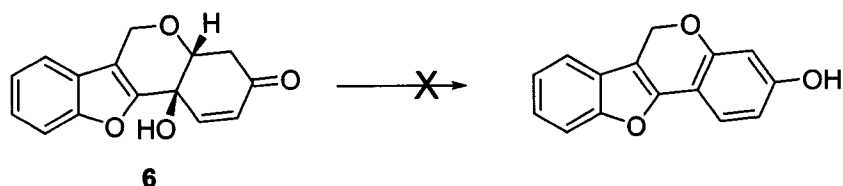
However, when the benzofuran anion was coupled with quinones substituted by methoxy, benzyloxy, phenylthio, or chloro groups or 2,5-dichloro-1,4-benzoquinone, the reactions gave messy results both with benzofuran monoanion or dianion. No desired hydroxycyclohexadienones were generated. Transmetalation with zirconium salts, a strategy used effectively in a related system,¹¹ did not result in the formation of the desired adduct.



Since the direct coupling with substituted quinones failed, we utilized the successful reactions from the model study. Modifications of the compounds **5** and **6** could afford the expected intermediates. Unfortunately, attempts to introduce the C-4–C-4a double bond (see Figure 1 for numbering) in ketone **6** by enol silyl ether formation and subsequent oxidation were unsuccessful, because the enol silyl ether could not be formed (TMSOTf, Et₃N; TMSCl, DBU; TMSI, HMDS).

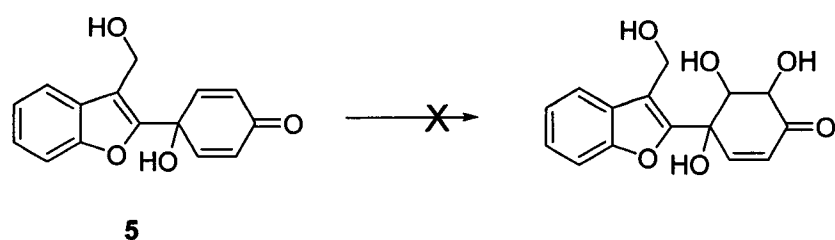
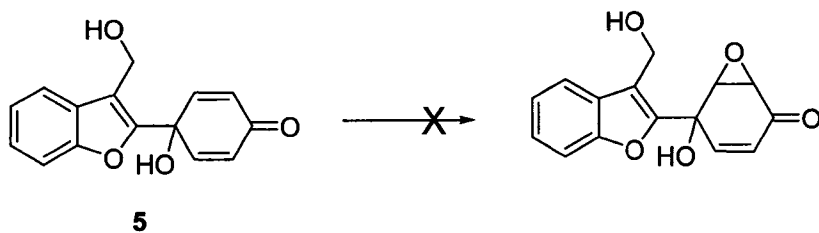


Dehydration to aromatize the cyclohexenone ring to a benzene ring was studied. The benzene ring could be oxidized back to a quinol later. Using PTSA in different solvents (methanol, ether, THF, or benzene), boron trifluoride diethyl etherate in benzene, or sulfuric acid in THF failed. Aromatization using methanesulfonyl chloride with Et₃N or pyridine; POCl₃ with Et₃N; or PBr₃ with Et₃N also failed.

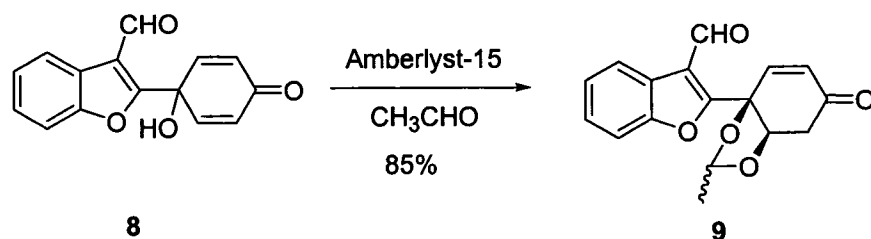
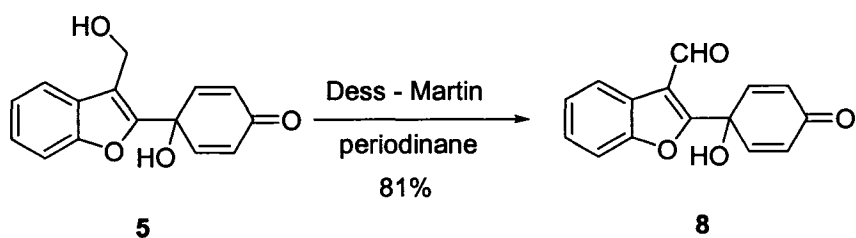


The reason for the above unsuccessful enol silyl ether formation and dehydration is also due to the bent and rigid geometry of **6**. To introduce another double bond in this rigid system is highly disfavored.

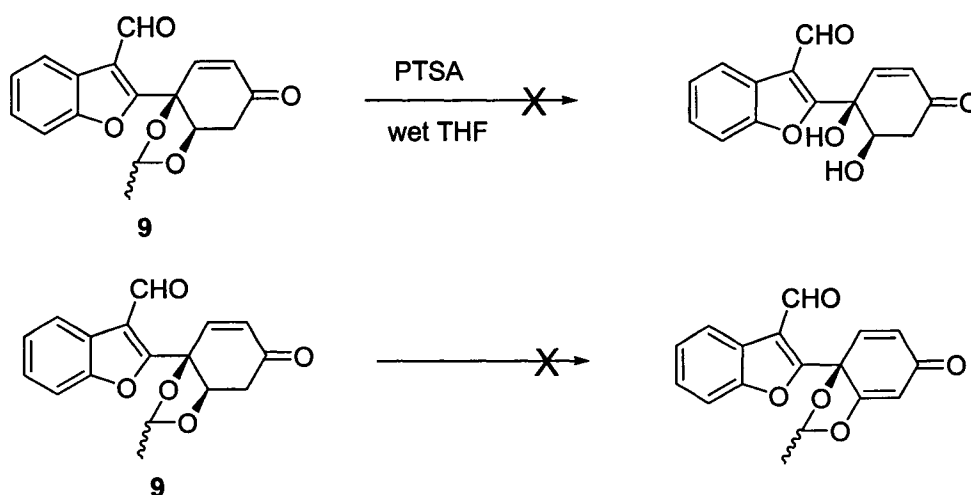
Another modification of compound **5** to introduce oxygen substituents by epoxidation using hydrogen peroxide or *tert*-butyl hydroperoxide with Triton B did not afford the epoxide product. The epoxidation by molybdenum hexacarbonyl and *tert*-butyl hydroperoxide in toluene at room temperature returned only starting materials. Other conditions to oxidize the double bond to a diol by OsO₄, NMO or PhI(OAc)₂, AcOH, failed.



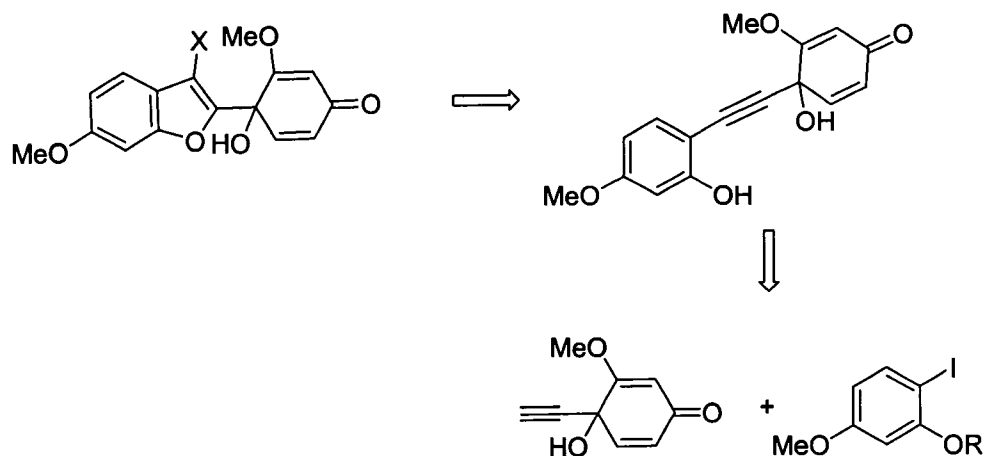
Although the enone double bond of compound **5** could not be oxidized, the primary alcohol of compound **5** was oxidized to an aldehyde using Dess-Martin periodinane to give compound **8** in 81% yield. In this case, the oxygen substituent was successfully introduced by Michael addition when compound **8** and acetaldehyde were treated with Amberlyst-15 resin in methylene chloride to give acetal **9** as a 1:1 ratio of diastereomers.



Surprisingly, acetal **9** was too stable to be deprotected even using PTSA in wet THF at 40 °C. Attempts to introduce another double bond by oxidation using IBX in DMSO and Na_2PdCl_4 , *t*-BuOOH in wet acetic acid also failed.

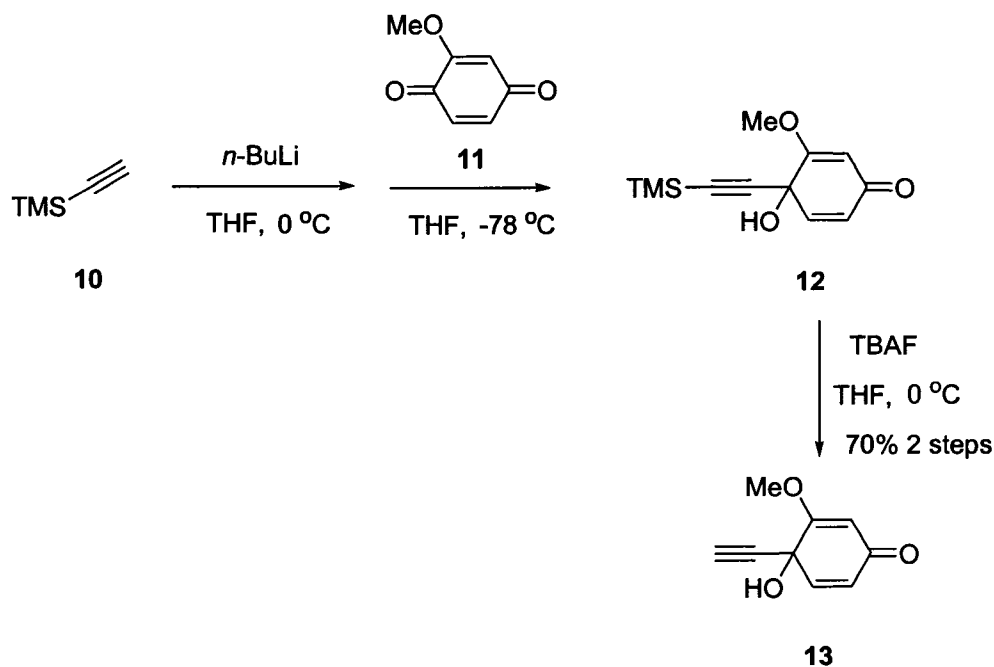


After extensive experimentation, we decided to change our synthetic strategy. For the following strategy, the furan moiety is planned from a phenol acetylene intermediate by a cyclization reaction. The phenol acetylene can be prepared by a palladium-catalyzed Sonogashira coupling.

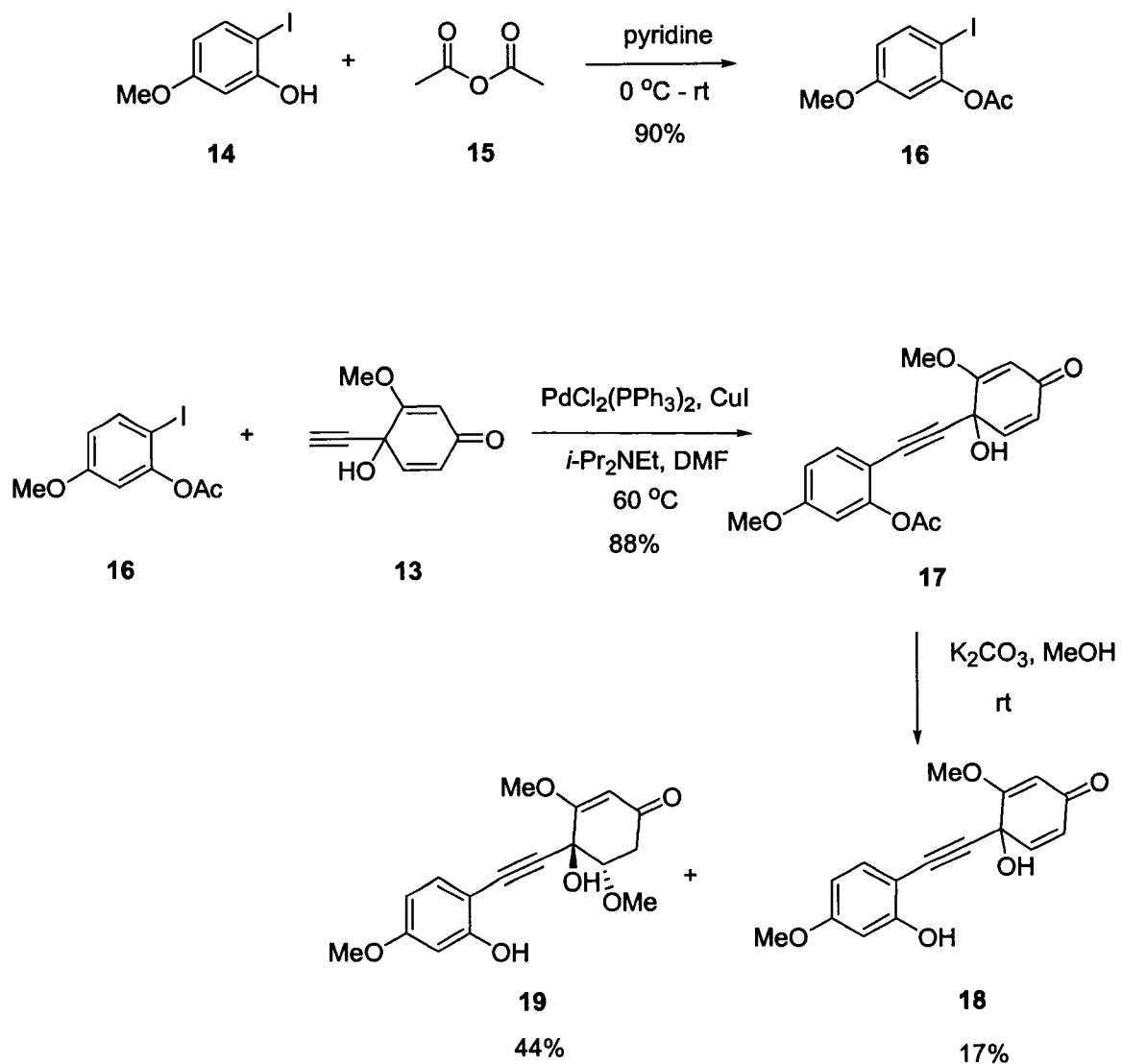


The commercially available trimethylsilylacetylene (**10**) was treated with *n*-butyl lithium, and reacted with 2-methoxy-1,4-benzoquinone (**11**)¹². In this case, the smaller lithium acetylide reacts very well with the substituted quinone to give quinol **12**.

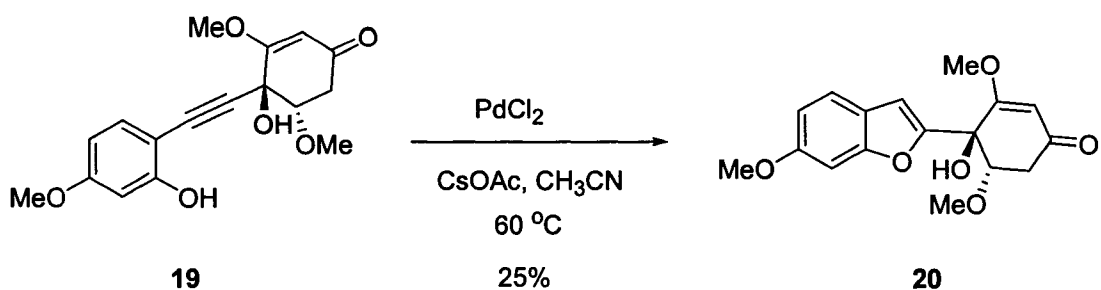
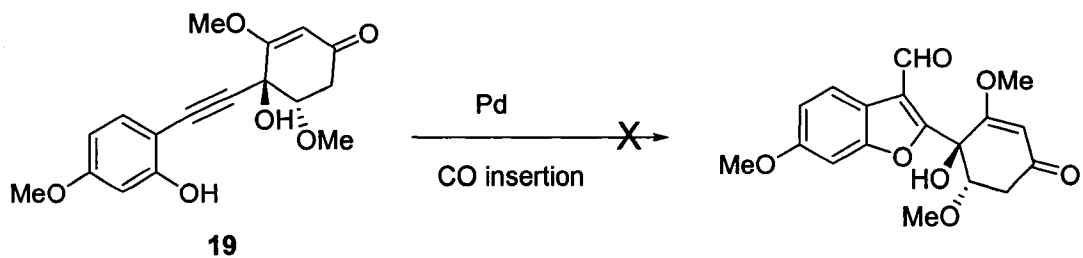
Deprotection of the trimethylsilyl group using tetrabutylammonium fluoride in THF at 0 °C provided compound **13** in excellent yield.



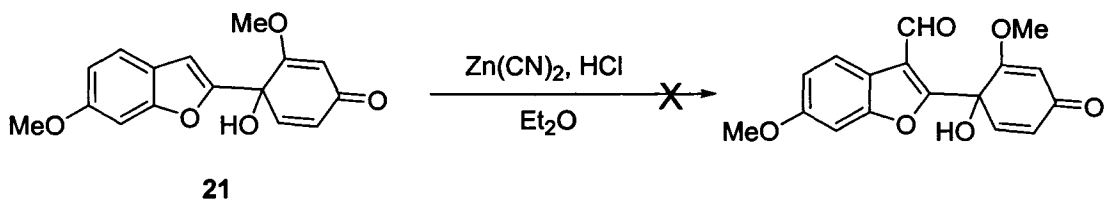
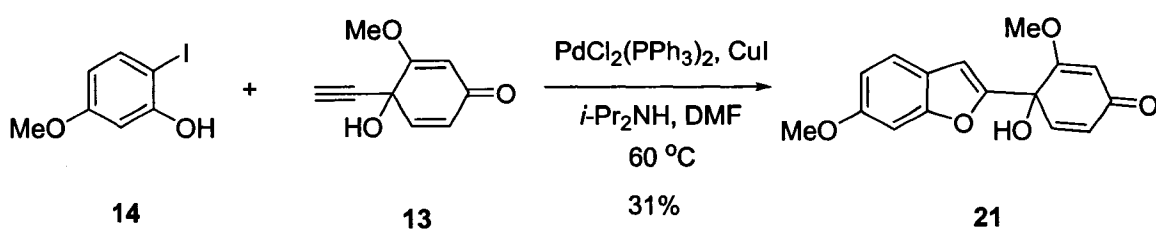
The hydroxyl group of 2-iodo-5-methoxy phenol (**14**)¹³ was protected by an acetyl group to give compound **16**, which undergoes Sonogashira coupling with acetylene **13** to afford compound **17**. However, the best conditions to remove the acetyl group (K_2CO_3 in methanol) gave the deprotected product **18** in 17% yield. The major product **19** has a methoxy group added to the enone. This methoxy group could be a protecting group for the double bond and may help avoid a possible regiochemical selectivity problem.

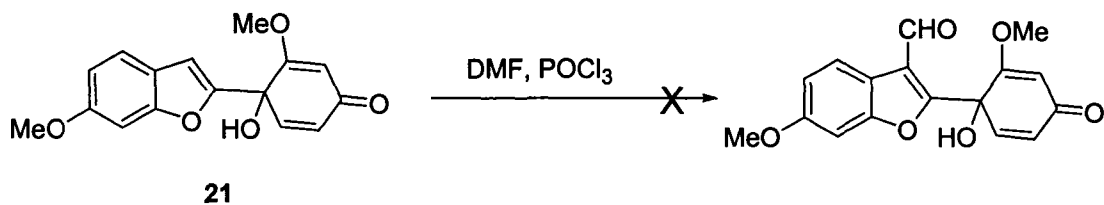


The palladium-catalyzed alkyne cyclization generated only benzofuran **20**. The *in situ* CO insertion was not achieved even though various Pd catalysts, ligands, and bases, such as PdCl₂, CuCl₂, K₂CO₃, and NaOAc in MeOH; PdCl₂, CsOAc in CH₃CN; PdCl₂(PPh₃)₂, dppp, and CsOAc in CH₃CN; PdI₂ and Cs₂CO₃ in MeOH; PdI₂-thiourea, CBr₄, and Cs₂CO₃ in MeOH, were tried.



The coupling of iodophenol **14** and alkyne **13** gave benzofuran **21** directly. Further modifications of **21** to introduce a formyl substituent on C-3 of the benzofuran,¹⁴ however, were unsuccessful.



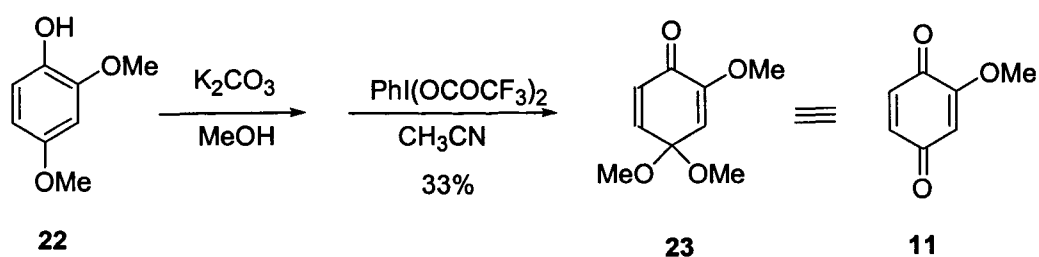


All of the strategies and numerous reactions that we attempted have led us to conclude:

1. benzofuran lithium anions couple with 1,4-benzoquinone well.
2. benzofuran lithium anions do not couple with substituted 1,4-benzoquinones.
3. lithium acetylides couple with substituted 1,4-benzoquinones well.

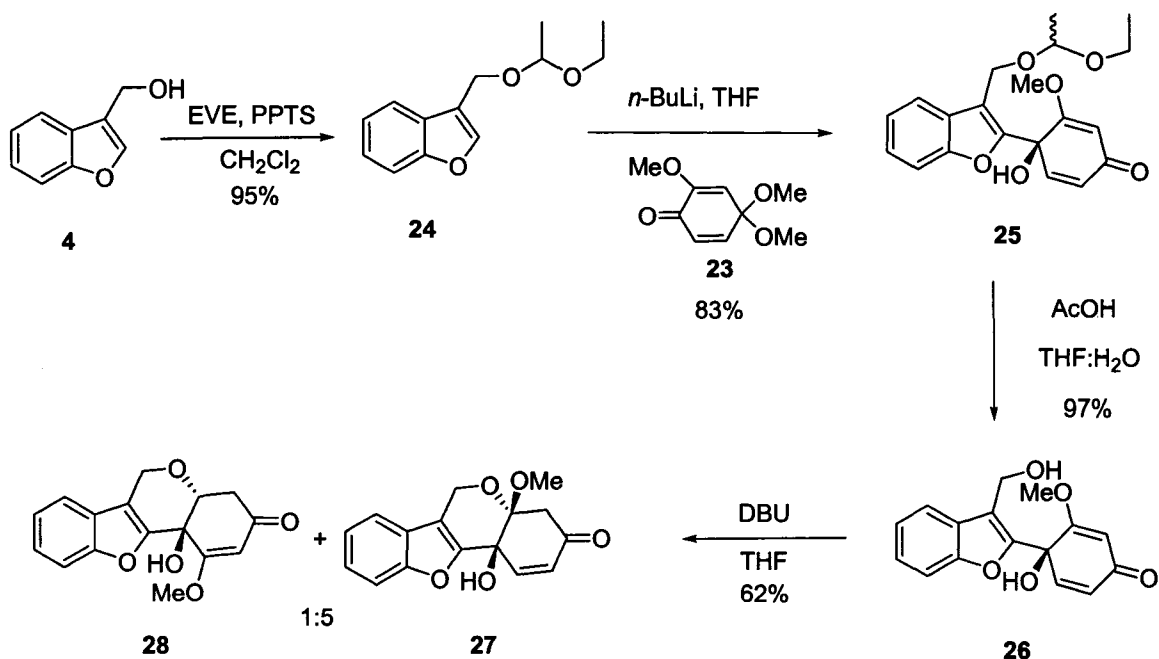
If benzofuran lithium anions are the reagents that must be used, the substituted 1,4-benzoquinones must be used in masked forms. This means that a substituted 1,4-benzoquinone equivalent must be introduced.

We next synthesized quinone monoketal **23**¹⁵ as a synthetic equivalent of methoxybenzoquinone (**11**).



The dianion of benzofuran **4** and quinone monoketal **23** afforded compound **26**, but the reaction was not clean and the yield was not sufficient. Once the primary alcohol in **4**

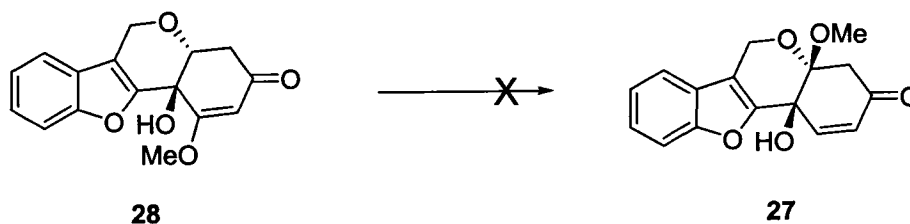
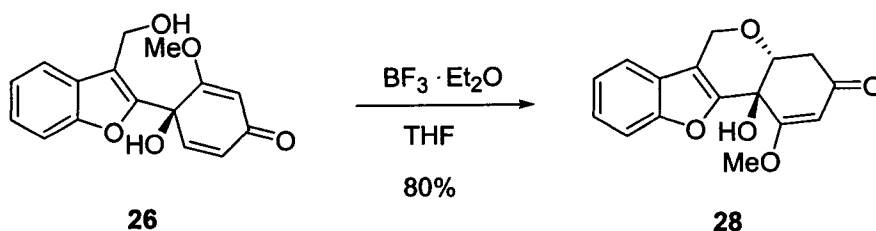
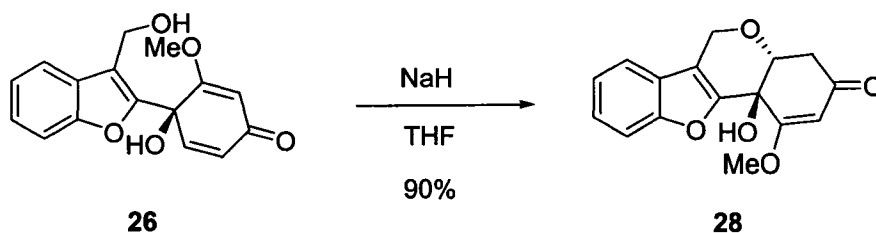
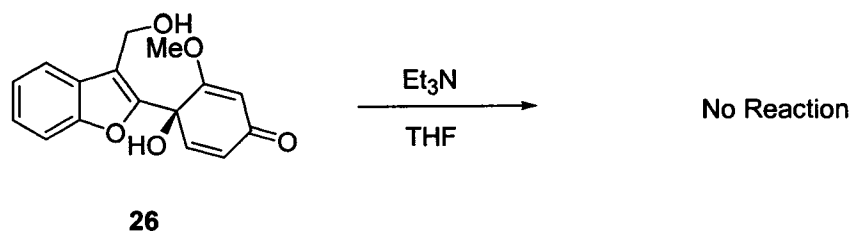
was protected by an ethyl vinyl ether group (EVE) to give compound **24**, the monoanion of **24** reacted with **23** to produce compound **25** in 83% yield. Compound **25** underwent deprotection to give compound **26** in excellent yield. Although there are two more steps, the overall yield of this strategy is higher than the dianion strategy.



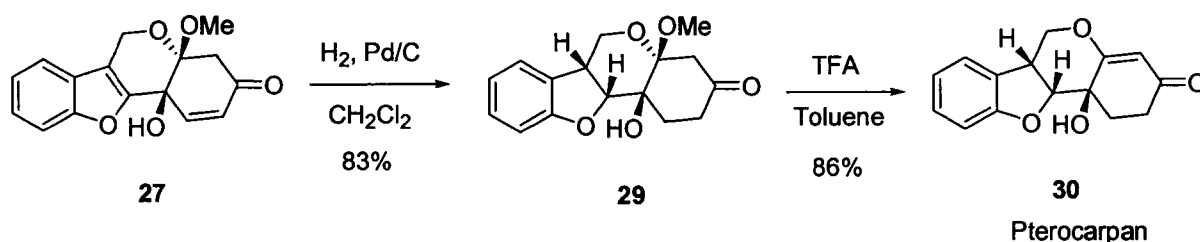
Cyclization of compound **26** using DBU in THF at 140 °C afforded adducts **27** and **28** in a 5:1 ratio in favor of the expected product **27**. The use of sodium hydride at 25 °C generated only **28**. The use of triethylamine at 140 °C returned only starting material. The use of acid catalysts, such as BF₃•Et₂O, afforded only **28**. Attempts to convert **28** into **27** using base catalysis (*t*-BuOK, DBU) were unsuccessful.

The presence of the methoxy group in compound **27** during these harsh conditions provides evidence that it is difficult to form an enol intermediate for this tetracyclic molecule.

The methoxy group, however, provides us advantages in the following synthesis. One advantage is that the presence of a methoxy group keeps the molecule as bent and rigid as the model system, which allows us to apply the stereoselective Pd/C-catalyzed hydrogenation. The other advantage is that the methoxy group can serve as a protecting group for the future enone double bond during the hydrogenation.



Catalytic hydrogenation of **27** using palladium on carbon affords compound **29** in 83% yield. After reduction of the double bonds, the geometry of compound **29** is no longer rigid. The methoxy group should be eliminated once an enol is formed. The treatment of the reduced product **29** with trifluoroacetic acid in toluene at 110 °C provided pterocarpan (**30**) in 86% yield.



The structure of **30** was supported by proton and carbon NMR, as well mass spectrometry. A 2-D NOE (Nuclear Overhauser Effect) experiment on the acetate of **30** showed interactions between the methyl group of the acetate and the hydrogens on C-1, C-11a, and C-6, supporting the relative stereochemistry assigned to **30**. The hydrogen on C-6a showed NOE interactions with the hydrogens on C-6, C-7 and C-11a.

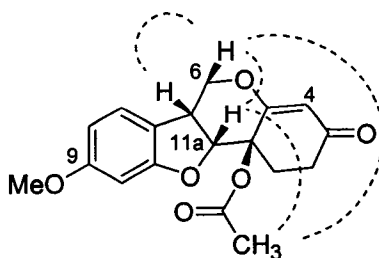


Figure 3. Observed 2-D NOE interaction

In conclusion, the synthesis of pterocarpin was achieved by a quinone-based route in only five steps. This route should be compatible with considerable structure variation. The use of quinone monoketal **23** as a synthetic equivalent of methoxybenzoquinone extended the range of quinols that can be produced by carbanion reactions. Certain heterocyclic quinol adducts show promising *in vivo* antitumor activity.¹⁶

Experimental Section

Unless stated otherwise, reactions were performed in flame-dried glassware under an argon atmosphere, using freshly distilled solvents. Diethyl ether (Et₂O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methylene chloride (CH₂Cl₂), benzene, toluene and diisopropylamine (*i*-Pr₂NH) were distilled from calcium hydride. *N,N*-Dimethyl formamide (DMF), dimethyl sulfoxide (DMSO), and hexamethylphosphoramide (HMPA) were distilled from calcium hydride and stored over activated 4 Å molecular sieves in sealed containers.

Unless stated otherwise, all reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) plates purchased from Aldrich (Cat. No. Z122785-25EA). Column or flash chromatography (silica) was performed with the indicated solvents using standard grade silica gel (particle size 230-400 mesh, 60 Å).

¹H and ¹³C NMR spectra were obtained on either a Varian 300 MHz or a Bruker 400 MHz spectrometer. Chemical shifts are reported relative to internal Me₄Si (¹H and ¹³C, δ 0.00 ppm) or chloroform (¹H, δ 7.26 ppm; ¹³C, δ 77.0 ppm). All melting points were obtained on a MEL-TEMP II variable temperature melting point apparatus from Laboratory Devices and are uncorrected. High-resolution mass spectra were recorded on a Kratos model

MS-50 spectrometer, and low-resolution mass spectra were recorded on a Finnegan 4023 mass spectrometer.

4-(Benzofuran-2-yl)-4-hydroxycyclohexa-2,5-dienone (3)

To benzofuran **1** (0.236 g, 2 mmol) in 10 mL of THF at -78 °C, was added *n*-BuLi (2.5M, 0.8 ml) dropwise. After five minutes at -78 °C, the temperature was increased to -15 °C and stirred for two hours. Then the above mixture was transferred slowly by cannula to the 1,4-benzoquinone **2** (0.216 g, 2 mmol) in 10 mL of THF at -78 °C. After five minutes at -78 °C, acetic acid (4 mmol) was added to quench the reaction. When the temperature was increased to 0 °C, 20 mL of H₂O was added and this was followed by ethyl acetate (20 mL × 2) extraction. The organic layers were washed with brine and dried with MgSO₄. Evaporation of solvent and purification by flash chromatography (hexane: ethyl acetate = 2:1) afforded compound **3**¹⁵ (0.43 g, 96% yield). ¹H NMR (300 MHz, CDCl₃) δ 3.9 (s, OH), 6.34 (d, *J* = 10.3 Hz, 2H), 6.77 (s, 1H), 7.16 (d, *J* = 10.3 Hz, 2H), 7.29 (m, 2H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 7.5 Hz, 1H). TLC (ethyl acetate: hexane = 1:1) R_f = 0.5.

4-Hydroxy-4-(3-hydroxymethylbenzofuran-2-yl)cyclohexa-2,5-dienone (5)

To benzofuran **4** (0.3 g, 2.03 mmol) in 20 mL of THF at -78 °C was added *n*-BuLi (2.5M, 2.03 mL) dropwise. After five minutes at -78 °C, the temperature was increased to 0 °C and stirred for one hour. Then the above mixture was transferred by cannula to the 1,4-benzoquinone **2** (0.55 g, 5.07 mmol) in 20 mL of THF at -78 °C slowly. After five minutes at -78 °C, the temperature was increased to 0 °C. Excess 0.5M aqueous acetic acid was added to quench the reaction, followed by H₂O, and ethyl acetate (20 mL × 2) extraction.

The organic layers were washed with brine and dried with MgSO_4 . Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 2:1) afforded compound **5** (0.37 g, 71% yield). ^1H NMR (300 MHz, CDCl_3) δ 4.26 (s, 2H), 6.17-6.22 (m, 2H), 6.95-7.00 (m, 2H), 7.19-7.27 (m, 2H), 7.34-7.37 (m, 1H), 7.46-7.48 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 55.05, 69.04, 111.69, 117.96, 119.55, 123.44, 125.57, 127.95, 128.15, 148.37, 150.45, 153.65, 186.26; MS m/z 256, 238, 181, 156; HRMS m/z for $\text{C}_{15}\text{H}_{12}\text{O}_4$ calcd. 256.0736, measured 256.0741. TLC (ethyl acetate: hexane: 1:1) R_f = 0.24.

11b-Hydroxy-6,11b-dihydro-4H,4aH-benzo[4,5]furo[3,2-c]chromen-3-one (6)

To compound **5** (0.28 g, 1.1 mmol) in 30 mL of THF at room temperature was added 60% NaH (2.2 mg, 0.055 mmol). The mixture was stirred at room temperature overnight. The solution was extracted by H_2O and ethyl acetate (20 mL \times 2). The organic layers were washed with brine and dried with MgSO_4 . Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 4:1) afforded compound **6** (0.244 g, 87% yield) as light yellow solid: m.p. 140 – 141 $^\circ\text{C}$. ^1H NMR (300 MHz, CD_3COCD_3) δ 2.63 & 2.69 (dd, J = 3.6, 0.9 Hz, 1H), 3.14 (dd, J = 16.2, 3.6 Hz, 1H), 4.34 (m, 1H), 4.90 (s, 2H), 5.60 (s, 1H, OH), 5.99 (dd, J = 10.2, 0.9 Hz, 1H), 7.02 (dd, 1H, J = 10.2, 2.1 Hz), 7.25-7.30 (m, 1H), 7.34-7.40 (m, 1H), 7.53-7.58 (m, 2H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 39.64, 62.41, 65.61, 79.22, 111.71, 115.87, 120.09, 123.30, 125.23, 125.35, 128.09, 143.98, 151.75, 155.30, 195.33; MS m/z 256, 185, 128, 84, 49; HRMS m/z for $\text{C}_{15}\text{H}_{12}\text{O}_4$ calcd. 256.0736, measured 256.0739. TLC (ethyl acetate: hexane = 1:2) R_f = 0.48.

11b-Hydroxy-1,4,4a,6a,11a,11b-hexahydro-2H,6H-benzo[4,5]furo[3,2-c]chromen-3-one (7)

The 25 mL round bottom flask, which contained compound **6** (30 mg, 0.117 mmol) and 3 mL of CH₂Cl₂, was evacuated by water aspirator until the solvent was bubbling and flushed with H₂ gas. This operation was repeated three times before the Pd/C (12 mg) addition. After the Pd/C addition, this evacuation / H₂ gas flush was repeated three times. The mixture was stirred under H₂ gas at room temperature overnight. When the reaction was complete, the mixture was filtered through Celite and the filtrate was concentrated and purified by flash chromatography (hexane: ethyl acetate = 2:1) to afford compound **7** (23 mg, 76% yield) as a colorless solid: m.p. 143-144.5 °C. ¹H NMR (300 MHz, CD₃COCD₃) δ 1.54 (td, *J* = 13.8, 5.1 Hz, 1H), 1.81-1.93 (m, 2H), 2.19-2.26 (m, 1H), 2.52-2.64 (m, 1H), 2.89 (dd, 1H, *J* = 15, 3.9 Hz), 3.70 (m, 1H), 3.75-3.80 (m, 1H), 4.02 (dd, *J* = 12.3, 5.1 Hz, 1H), 4.44 (d, *J* = 12.3 Hz, 1H), 4.79 (s, 1H, OH), 5.02 (d, *J* = 9.3 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.87 (td, *J* = 7.5 Hz, *J* = 0.9 Hz, 1H), 7.10-7.16 (m, 1H), 7.19-7.22 (m, 1H); ¹³C NMR (75 MHz, CD₃COCD₃) δ 28.71, 36.07, 41.92, 42.17, 65.84, 71.06, 79.41, 88.82, 109.12, 120.81, 122.99, 128.58, 129.56, 160.86, 207.87. TLC (ethyl acetate: hexane = 1:1) R_f = 0.25.

2-(1-Hydroxy-4-oxocyclohexa-2,5-dienyl) benzofuran-3-carbaldehyde (8)

To compound **7** (60 mg, 0.234 mmol) in 7 mL of CH₂Cl₂ at 0 °C was added Dess-Martin periodinane (0.1 g, 0.236 mmol). The mixture was stirred at 0 °C for two hours. The solution was partitioned between CH₂Cl₂ and brine. The organic layers were washed with brine and dried with MgSO₄. The solvent was removed by vacuum evaporation and the residue was purified by silica gel flash chromatography (hexane: ethyl acetate = 3:1) to

afford compound **8** (48 mg, 81% yield): ^1H NMR (300 MHz, CDCl_3) δ 6.35 (m, 1H), 6.38 (m, 1H), 7.01 (m, 1H), 7.04 (m, 1H), 7.37-7.42 (m, 2H), 7.44-7.49 (m, 1H), 8.07-8.11 (m, 1H), 10.60 (s, 1H).

2-(2-Methyl-6-oxo-7, 7a-dihydro-6H-benzo[1,3]dioxol-3a-yl)benzofuran-3-carbaldehyde (9)

To compound **8** (22 mg, 0.086 mmol) in 5 mL of CH_2Cl_2 was added 10 mg Amberlyst-15. The above mixture was cooled to 0 °C and followed by the addition of excess acetaldehyde (0.2 mL). The temperature was increased slowly to room temperature. The solution was partitioned between CH_2Cl_2 and brine. The organic layers were washed with brine and dried with MgSO_4 . The solvent was removed by vacuum evaporation and the residue was purified by silica gel flash chromatography (hexane: ethyl acetate = 3:1) to afford compound **9** (22 mg, 85% yield): ^1H NMR (300 MHz, CDCl_3) δ 1.50 & 1.52 (d, J = 0.6 Hz, 3H), 3.08-3.18 (m, 2H), 4.73 (m, 1H), 5.49 (m, 1H), 6.16 & 6.32 (d, J = 7.5 Hz, 1H), 6.61-6.62 & 6.63-6.64 (m, 1H), 7.38-7.41 (m, 2H), 7.45-7.47 (m, 1H), 8.27-8.30 (m, 1H), 10.70 & 10.73 (s, 1H).

4-Hydroxy-3-methoxy-4-(trimethylsilylethynyl)cyclohexa-2,5-dienone (12)

To trimethylsilylacetylene **10** (50 mg, 0.5 mmol) in 10 mL of THF at 0 °C was added slowly *n*-BuLi (2.5M, 0.5 mmol). The mixture was stirred at 0 °C for one hour and cooled to -78 °C. At -78 °C, 2-methoxy-1,4-benzoquinone (**11**) (76 mg, 0.55 mmol) in 2 mL of THF was added slowly to the lithium reagent. After 5 minutes, excess AcOH was added to quench the reaction. After the temperature was increased to 0 °C, the solution was partitioned between H_2O and ethyl acetate (10 mL \times 2). The organic layers were washed with brine and

dried with MgSO_4 . Evaporation of the solvent under vacuum gave the crude product **12**, which was used directly in the next step.

4-Ethynyl-4-hydroxy-3-methoxycyclohexa-2,5-dienone (13)

To the crude compound **12** (about 0.5 mmol) in 10 mL of THF at 0 °C was added TBAF (1M, 0.5 mL). The mixture was stirred and warmed to room temperature slowly. 0.5M AcOH was used to neutralize the solution, which was partitioned between H_2O and ethyl acetate (10 mL \times 2). The organic layers were washed with brine and dried with MgSO_4 . The solvent was removed by vacuum evaporation and the residue was purified by silica gel flash chromatography (hexane: ethyl acetate = 2:3) to afford compound **13** (57 mg, 70% yield over two steps). ^1H NMR (300 MHz, CDCl_3) δ 2.57 (s, 1H), 3.86 (s, 3H), 5.52 (d, J = 1.5 Hz, 1H), 6.16 (dd, 1H, J = 9.9, 1.5 Hz), 6.72 (d, J = 9.9 Hz, 1H).

2-Iodo-5-methoxyphenyl acetate (16)

To 2-iodo-5-methoxyphenol (**14**) (1.1 g, 4.4 mmol) in 50 mL of pyridine at 0 °C was slowly added acetyl anhydride (**15**) (0.9 g, 8.8 mmol). The mixture was warmed slowly to room temperature and stirred overnight. Vacuum evaporation removed most of the solvent, which was followed by the addition of 1M HCl. The solution was partitioned between H_2O and CH_2Cl_2 (20 mL \times 3). The organic layers were washed with brine and dried with MgSO_4 . Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 9:1) afforded compound **16** (1.1 g, 90% yield). ^1H NMR (300 MHz, CDCl_3) δ 3.79 (s, 3H), 6.62 (dd, J = 8.7, 3.0 Hz, 1H), 6.69 (d, J = 3.0 Hz, 1H), 7.67 (d, J = 8.7 Hz, 1H).

2-(1-Hydroxy-2-methoxy-4-oxocyclohexa-2,5-dienylethynyl)-5-methoxy-phenyl acetate (17)

To compound **16** (0.51 g, 1.8 mmol) and compound **13** (0.3 g, 1.83 mmol) in 8 mL of DMF was added $\text{PdCl}_2(\text{PPh}_3)_2$ (63 mg, 0.09 mmol), CuI (17 mg, 0.09 mmol), and diisopropylamine (0.27 g, 2.7 mmol). Under an argon atmosphere, the mixture was heated to 60 °C for two hours. After the mixture was cooled to room temperature, it was extracted by H_2O and ethyl acetate (20 mL \times 2). The organic layers were washed with brine and dried with MgSO_4 . Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 2:3) afforded compound **17** (0.51 g, 88% yield). ^1H NMR (300 MHz, CDCl_3) δ 2.28 (s, 3H), 3.81 (s, 3H), 3.87 (s, 3H), 5.53 (d, J = 1.5 Hz, 1H), 6.18 (dd, J = 9.9, 1.5 Hz, 1H), 6.63 (d, J = 2.4 Hz, 1H), 6.73-6.77 (m, 2H), 7.39 (d, J = 9.9 Hz, 1H).

4-Hydroxy-4-(2-hydroxy-4-methoxyphenylethynyl)-3-methoxycyclohexa-2,5-dienone (18) and 4-hydroxy-4-(2-hydroxy-4-methoxyphenylethynyl)-3,5-dimethoxycyclohex-2-enone (19)

To compound **17** (0.7 g, 2.2 mmol) in methanol was added anhydrous K_2CO_3 (1.2 g, 8.8 mmol) at room temperature and the mixture was stirred overnight at room temperature. Excess AcOH was added to neutralize the solution. The solution was partitioned between H_2O and ethyl acetate (10 mL \times 2). The organic layers were washed with brine and dried with MgSO_4 . The solvent was removed and the residue was purified by silica gel flash chromatography (hexane: ethyl acetate = 1:1) to afford compound **18** (0.11 g, yield 17%) and compound **19** (0.30 g, 44% yield).

4-Hydroxy-4-(2-hydroxy-4-methoxyphenylethynyl)-3-methoxycyclohexa-2,5-dienone

(18) ^1H NMR (300 MHz, CD_3COCD_3) δ 3.77 (s, 3H), 3.86 (s, 3H), 5.47 (d, $J = 1.5$ Hz, 1H), 6.02 (dd, $J = 9.9, 1.5$ Hz, 1H), 6.43-6.47 (m, 2H), 6.83 (d, $J = 9.9$ Hz, 1H), 7.22 (dd, $J = 8.1, 0.6$ Hz, 1H).

4-Hydroxy-4-(2-hydroxy-4-methoxyphenylethynyl)-3,5-dimethoxycyclohex-2-enone (19)

^1H NMR (300 MHz, CDCl_3) δ 2.78-2.92 (m, 2H), 3.56 (s, 3H), 3.79 (s, 3H), 3.84 (s, 3H), 3.96-3.98 (m, 1H), 5.44 (s, 1H), 6.44 (dd, $J = 8.1, 2.4$ Hz, 1H), 6.48 (d, $J = 2.4$ Hz, 1H), 7.21 (d, $J = 8.1$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 38.9, 50.8, 55.6, 57.2, 58.8, 70.0, 81.9, 82.2, 100.7, 101.0, 102.1, 107.2, 133.0, 159.5, 162.3, 172.7, 195.9.

4-Hydroxy-3,5-dimethoxy-4-(6-methoxybenzofuran-2-yl)cyclohex-2-enone (20)

To compound 19 (40 mg, 0.13 mmol) in 10 mL of acetonitrile was added PdCl_2 (23 mg, 0.13 mmol) and CsOAc (0.1 g, 0.52 mmol). The mixture was heated to 60 $^\circ\text{C}$ under an argon atmosphere overnight. The mixture was cooled to room temperature and filtered through Celite. The filtrate was concentrated and purified by silica gel flash chromatography (hexane: ethyl acetate = 1:2) to afford compound 20 (10 mg, 25% yield). ^1H NMR (300 MHz, CDCl_3) δ 2.66 (dd, $J = 17.1, 3.3$ Hz, 1H), 2.82 (dd, $J = 17.1, 5.1$ Hz, 1H), 3.45 (s, 3H), 3.80 (s, 3H), 3.85 (s, 3H), 4.17 (m, 1H), 5.60 (s, 1H), 6.74 (d, $J = 0.9$ Hz, 1H), 6.88 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.00 (d, $J = 2.4$ Hz, 1H), 7.42 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 38.5, 55.9, 57.0, 58.4, 73.7, 80.6, 96.2, 103.9, 106.0, 107.6, 112.6, 121.6, 153.9, 156.2, 158.6, 172.2, 195.2.

4-Hydroxy-3-methoxy-4-(6-methoxybenzofuran-2-yl)cyclohexa-2,5-dienone (21)

To compound **14** (25 mg, 0.1 mmol) and compound **13** (16 mg, 0.1 mmol) in 3 mL of DMF was added a trace of $\text{PdCl}_2(\text{PPh}_3)_2$, a trace of CuI, and diisopropylamine (50 mg, 0.5 mmol). Under an argon atmosphere, the mixture was heated to 60 °C for 20 hours. After the mixture was cooled to room temperature, it was extracted by H_2O and ethyl acetate (10 mL \times 2). The organic layers were washed with brine, and dried with MgSO_4 . Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 1:1) afforded compound **21** (9 mg, 31% yield). ^1H NMR (300 MHz, CDCl_3) δ 3.78 (s, 3H), 3.87 (s, 3H), 5.56 (d, J = 1.8 Hz, 1H), 6.20 (dd, J = 9.9, 1.8 Hz, 1H), 6.43 (dd, J = 9.9, 2.4 Hz, 1H), 6.48 (d, J = 8.4 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 9.9 Hz, 1H).

2,4,4-Trimethoxy-cyclohexa-2,5-dienone (23)

To 2,4-dimethoxyphenol (**22**) (0.33 g, 2.1 mmol) in 12 mL of methanol at room temperature was added anhydrous K_2CO_3 (0.58 g, 4.2 mmol) and the mixture was stirred at room temperature for 30 minutes. To the above mixture, [bis(trifluoroacetoxy)-iodo]benzene (0.9 g, 2.1 mmol) in 6 mL of acetonitrile was added slowly. After the addition, the color of the solution became brown. After 10 more minutes, the solution became dark. At this point, H_2O was added and the solution was extracted by Et_2O (20 mL \times 2). The organic layers were washed with brine and dried with MgSO_4 . Evaporation of solvent and purification by flash chromatography (hexane: ethyl acetate = 1:1) afforded compound **23** (0.12 g, 33% yield) as yellow crystals: m.p. 56 - 58.5 °C; ^1H NMR (400 MHz, CDCl_3) δ 3.37 (s, 6H), 3.71 (s, 3H), 5.68 (d, J = 2.8 Hz, 1H), 6.28 (d, J = 10.0 Hz, 1H), 6.83 (dd, J = 10.0, 2.8 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 50.6, 55.2, 95.8, 110.1, 128.9, 144.3, 151.7, 180.6; MS m/z 184,

169, 168, 153, 152, 124; HRMS m/z for $C_9H_{12}O_4$ calcd. 184.0736, measured 184.0738.

TLC (ethyl acetate: hexane = 1:1) R_f = 0.36.

3-(1-Ethoxy-ethoxymethyl)benzofuran (24)

To compound **4** (0.17 g, 1.15 mmol) in 20 mL of CH_2Cl_2 at room temperature was added ethyl vinyl ether (0.25 g, 3.45 mmol) and pyridinium *p*-toluenesulfonate (29 mg, 0.115 mmol). After one hour at room temperature, the solution was washed with saturated aqueous $NaHCO_3$, brine, and dried with $MgSO_4$. Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 6:1) afforded compound **24** (0.24 g, 95% yield). 1H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3H), 1.39 (d, J = 5.4 Hz, 3H), 3.56 (m, 1H), 3.70 (m, 1H), 4.74 (q, J = 35.1, 12 Hz, 2H), 4.87 (q, J = 5.4 Hz, 1H), 7.29 (m, 2H), 7.49 (m, 1H), 7.62 (s, 1H), 7.66 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.6, 20.0, 57.9, 60.7, 99.1, 111.7, 118.1, 120.3, 122.9, 124.7, 127.4, 143.1, 155.8; MS m/z 220, 176, 175, 131, 130; HRMS m/z for $C_{13}H_{16}O_3$ calcd. 220.1099, measured 220.1102. TLC (ethyl acetate: hexane = 1:2) R_f = 0.69.

4-[3-(1-Ethoxyethoxymethyl)benzofuran-2-yl]-4-hydroxy-3-methoxycyclohexa-2, 5-dienone (25)

To compound **24** (0.11 g, 0.5 mmol) in 10 mL of THF at $-78^\circ C$ was slowly added *n*-BuLi (2.5M, 0.24 mL, 0.6 mmol). After 10 minutes at $-78^\circ C$, the temperature was increased to $0^\circ C$ and the mixture was stirred for 1 h. Then the above lithium reagent was slowly transferred by cannula to **23** in 10 mL of THF at $-78^\circ C$. After 10 min, 0.035 mL glacial AcOH was added to the solution at $-78^\circ C$. The solution was warmed to $0^\circ C$ and extracted

with brine and ethyl acetate (15 mL \times 3). Organic layers were combined, washed with brine, and dried with anhydrous MgSO_4 . Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 2:1) afforded compound **25** as a yellow oil (0.15 g, 83% yield). ^1H NMR (300 MHz, CDCl_3) δ 1.22 (td, J = 7.2, 3.6 Hz, 3H), 1.37 (dd, J = 7.2, 5.4 Hz, 3H), 3.58(m, 2H), 3.73 (d, J = 3.0 Hz, 3H), 4.90 (m, 1H), 4.98(m, 2H), 5.64 (m, 1H), 6.20 (m, 1H), 6.69 (t, J = 9.0 Hz, 1H), 7.26 (m, 2H), 7.36 (m, 1H), 7.59 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 15.3&15.5, 19.5&19.8, 56.4, 56.7&57.1, 59.5&60.5, 70.9&71.0, 99.1, 101.9&102.0, 111.6&111.7, 115.3&115.8, 119.6&119.9, 123.3, 125.3&125.4, 127.7, 128.7, 143.5&143.6, 151.5&151.8, 153.8&153.9, 172.7&172.8, 187.6&187.7. TLC (ethyl acetate: hexane = 1:1) R_f = 0.1.

4-Hydroxy-4-[3-(hydroxymethyl)benzofuran-2-yl]-3-methoxycyclohexa-2,5-dienone (26)

To compound **25** (90 mg, 0.25 mmol) in 5mL of THF and 5mL of H_2O at room temperature was added 1mL of AcOH. The solution was heated to 40 $^\circ\text{C}$ for 8 hours until the reaction was complete. The solution was cooled to room temperature and extracted with brine and ethyl acetate (10 mL \times 3). Organic layers were combined, washed with brine, and dried with anhydrous MgSO_4 . Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 1:2) afforded compound **26** as brown colored solid (77 mg, 97% yield). ^1H NMR (300 MHz, CDCl_3) δ 3.64 (s, 3H), 4.95 (q, J = 18.6, 12.9 Hz, 2H), 5.56 (d, J = 1.5 Hz, 1H), 6.12 (dd, J = 9.9, 1.5 Hz, 1H), 6.71 (d, J = 9.9 Hz, 1H), 7.24 (m, 2H), 7.32 (m, 2H), 7.49 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 54.9, 56.5, 70.7, 101.8, 111.6, 118.8, 119.6, 123.3, 125.4, 127.1, 128.2, 144.6, 150.6, 153.7, 173.6, 188.3; MS m/z

287 (M+1), 286, 268, 267; HRMS m/z for $C_{16}H_{14}O_5$ calcd. 286.0841, measured: 286.0845.

TLC (ethyl acetate: hexane = 2:1) R_f = 0.22.

11b-Hydroxy-4a-methoxy-6,11b-dihydro-4H,4aH-benzo[4,5]furo [3,2-c]chromen-3-one (27) and 11b-hydroxy-1-methoxy-6,11b-dihydro-4H,4aH-benzo[4,5]furo[3,2-c]chromen-3-one (28)

The compound **26** (32 mg, 0.11 mmol) in 5mL of THF was saturated with argon for 5 minutes. During the bubbling process, DBU (5 mg, 0.033 mmol) was added at room temperature. The sealed tube was heated to 140 °C for 4 hours. The solution was cooled to room temperature, neutralized by 0.5M aqueous AcOH, and extracted by H₂O and ethyl acetate (10 mL × 2). Organic layers were combined, washed with brine, and dried with anhydrous MgSO₄. Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 1:2) afforded compound **27** (16.5 mg), compound **28** (3.3 mg), and recovered starting material **26** (10.5 mg). The overall yield was 62%, conversion yield was 92%.

11b-Hydroxy-4a-methoxy-6,11b-dihydro-4H,4aH-benzo [4,5] furo [3,2-c] chromen-3-one (27) ¹H NMR (300 MHz, CDCl₃) δ 3.03 (s, 2H), 3.49 (s, 3H), 4.78 (s, 2H), 6.06 (d, J = 10.2 Hz, 1H), 6.97 (d, J = 10.2 Hz, 1H), 7.25 (m, 1H), 7.35 (m, 2H), 7.54 (d, J = 8.1 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 42.2, 50.1, 58.9, 68.3, 100.2, 112.2, 114.4, 119.7, 123.5, 124.9, 125.4, 127.8, 143.5, 148.6, 155.5, 195.4; MS m/z 286, 285, 254, 253, 212, 211, 184, 156, 127, 102, 77; HRMS m/z for $C_{16}H_{14}O_5$ calcd. 286.0841, measured 286.0845. TLC (ethyl acetate: hexane = 2:1) R_f = 0.75.

11b-Hydroxy-1-methoxy-6,11b-dihydro-4H,4aH-benzo[4,5]furo[3,2-c]chromen-3-one

(28) ^1H NMR (300 MHz, CDCl_3) δ 2.72 (dd, $J = 16.5, 3.9$ Hz, 1H), 3.04 (dd, $J = 16.5, 3.9$ Hz, 1H), 3.75 (s, 3H), 4.18 (t, $J = 3.9$ Hz, 1H), 4.88 (s, 2H), 5.42 (s, 1H), 7.26 (td, $J = 7.5, 0.9$ Hz, 1H), 7.35 (td, $J = 8.1, 0.9$ Hz, 1H), 7.41 (d, $J = 7.5$ Hz, 1H), 7.54 (d, $J = 8.1$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 38.8, 56.7, 62.9, 68.5, 77.9, 101.8, 112.2, 115.7, 119.9, 123.4, 124.8, 125.5, 149.4, 155.6, 172.3, 195.7; MS m/z 286, 285, 182, 181, 130, 85, 83; HRMS m/z for $\text{C}_{16}\text{H}_{14}\text{O}_5$ calcd. 286.0841, measured 286.0845. TLC (ethyl acetate: hexane = 2:1) R_f = 0.42.

11b-Hydroxy-1-methoxy-6,11b-dihydro-4H,4aH-benzo[4,5]furo[3,2-c]chromen-3-one
(28)

To compound **26** (6 mg) in 3 mL of THF at room temperature was added a trace of NaH and stirred overnight. The 0.5M aqueous AcOH was added to neutralize the solution, which was extracted by H_2O and ethyl acetate (10 mL \times 2). Organic layers were combined, washed with brine, and dried with anhydrous MgSO_4 . Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 1:2) afforded compound **28** (5.4 mg, 90% yield).

11b-Hydroxy-1-methoxy-6,11b-dihydro-4H,4aH-benzo[4,5]furo[3,2-c]chromen-3-one
(28)

The solution of compound **26** (15 mg, 0.052 mmol) in 5mL of THF was saturated with argon for 5 minutes. During the bubbling process, boron trifluoride diethyl etherate (7.4 mg, 0.052 mmol) was added. After the addition, the argon bubbling continued 5 more

minutes. The mixture was stirred at room temperature for 5 hours without any product formed. The temperature was increased to 70 °C and stirred overnight, and there was no product by the TLC monitoring. When the mixture was heated to 140 °C for 2 hours, TLC monitoring showed the reaction was completed. The solution was cooled to room temperature, and extracted by H₂O and ethyl acetate (10 mL × 2). Organic layers were combined, washed with brine, and dried with anhydrous MgSO₄. Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 1:2) afforded compound **28** (12 mg, 80% yield).

11b-Hydroxy-4a-methoxy-1,4,4a,6a,11a,11b-hexahydro-2H,6H-benzo[4,5]furo[3,2-c]chromen-3-one (29)

The flask contained compound **27** (30 mg, 0.1 mmol) and 20 mL of CH₂Cl₂ was evacuated by water aspirator until the solvent was bubbling and then flushed with hydrogen gas. This operation was repeated three times before the Pd/C (50 mg) addition. After the Pd/C addition, this evacuation / H₂ gas flush was repeated three times. The mixture was stirred under H₂ gas at room temperature overnight. When the reaction was complete, the mixture was filtered through Celite. The filtrate was concentrated and purified by flash chromatography (hexane: ethyl acetate = 2:1) to afford compound **29** (25 mg, yield 83%) ¹H NMR (300 MHz, CDCl₃) δ 1.96 (m, 1H), 2.18 (m, 2H), 2.57 (m, 1H), 2.75 (q, *J* = 39.3, 15.3 Hz, 2H), 3.29 (s, 3H), 3.70 (dd, *J* = 5.1, 9.0 Hz, 1H), 3.82 (dd, *J* = 11.4, 1.5 Hz, 1H), 4.09(q, *J* = 5.4 Hz, 1H), 5.01 (d, *J* = 9.3 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.90 (t, *J* = 7.2 Hz, 1H), 7.15 (m, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 30.1, 35.3, 40.5, 45.7, 48.6, 61.7, 72.0, 85.0, 99.9, 109.6, 121.5, 124.0, 129.2, 129.5, 159.8, 208.0; MS *m/z* 290, 289, 215, 160, 141, 130,

128, 117; HRMS m/z for $C_{16}H_{18}O_5$ calcd. 290.1154, measured 290.1158. TLC (ethyl acetate: hexane = 2:1) R_f = 0.40.

Pterocarpan (30)

To compound **29** (40 mg, 0.14 mmol) in 20 mL of toluene was added trifluoroacetic acid (0.2 mL), then heated to reflux for 0.5 hour. The solution was cooled to room temperature, washed with saturated $NaHCO_3$ solution, brine, and dried with $MgSO_4$. Evaporation and purification by flash chromatography (hexane: ethyl acetate = 1:2) afforded compound **30** (31 mg, yield 86%) as a colorless solid: m.p. 198 - 200 °C; 1H NMR (300 MHz, CD_3COCD_3) δ 2.03 (m, 1H), 2.27 (m, 1H), 2.73 (m, 2H), 4.04 (m, 1H), 4.30 (d, J = 10.8 Hz, 1H), 4.84 (dd, J = 10.8, 4.2 Hz, 1H), 4.97 (d, J = 10.8 Hz, 1H), 5.25 (s, OH), 5.42 (s, 1H), 6.73 (d, J = 8.1 Hz, 1H), 6.92 (t, J = 7.5 Hz, 1H), 7.15 (t, J = 8.1 Hz, 1H), 7.37 (d, J = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 32.1, 32.2, 40.6, 67.3, 67.7, 82.4, 108.2, 109.1, 121.4, 125.0, 128.7, 129.1, 159.5, 171.6, 197.1; MS m/z 258, 257, 172, 131, 130, 117; HRMS m/z for $C_{15}H_{14}O_4$ calcd. 258.0892, measured 258.0897. TLC (ethyl acetate: hexane = 2:1) R_f = 0.25.

References:

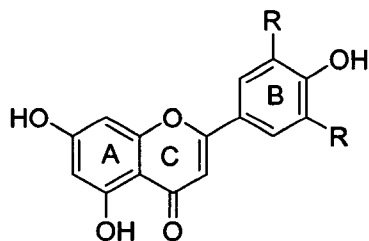
1. Kuroyanagi, M.; Arakawa, T.; Hirayama, Y.; Hayashi, T. *J. Natural Prod.* **1999**, *62*, 1595-1599.
2. Barrero, A. F.; Cabrera, E.; Garcia, I. R. *Phytochemistry* **1998**, *48*, 187-190.
3. Soby, S.; Caldera, S.; Bates, R.; VanEtten, H. *Phytochemistry* **1996**, *41*, 759-765.

4. Miyase, T.; Sano, M.; Nakai, H.; Muraoka, M.; Nakazawa, M.; Suzuki, M.; Yoshino, K.; Nishihara, Y.; Tanai, J. *Phytochemistry* **1999**, *52*, 303-310.
5. Kraus, G. A.; Wei, J. *J. Nat. Prod.* **2004**, *67*, 1039-1140.
6. Crabtree, R. H.; Davis, M. W. *Organometallics* **1983**, *2*, 681-682; Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866-3868.
7. Bishop, B. C.; Cottrell, I. F.; Hands, D. *Synthesis* **1997**, 1315-1320.
8. Liotta, D.; Saindane, M.; Barnum, C. *J. Org. Chem.* **1981**, *46*, 3369-3370.
9. Wells, G.; Berry, J. M.; Bradshaw, T. D.; Burger, A. M.; Seaton, A.; Wang, B.; Westwell, A. D.; Stevens, M. F. G. *J. Med. Chem.* **2003**, *46*, 532-541.
10. Structural data has been sent to the Cambridge X-ray database.
11. Corey, E. J.; Wu, L. I. *Tetrahedron Lett.* **1994**, *35*, 663-664.
12. Hua, Duy H.; Tamura, Masafumi; Huang, Xiaodong; Stephany, Heidi A.; Helfrich, Brian A.; Perchellet, Elisabeth M.; Sperfslage, Bonnie J.; Perchellet, Jean-Pierre; Jiang, Suping; Kyle, Dennis E.; Chiang, Peter, K. *J. Org. Chem.* **2002**, *67*, 2907-2912.
13. Tsukayama, M.; Utsumi, H.; Kunugi, A.; Nozaki, H. *Heterocycles* **1997**, *45*, 1131-1142.
14. (a) Yang, Zh.; Liu, H.; Lee, C.; Chang, H.; Wong, H. N. C. *J. Org. Chem.* **1992**, *57*, 7248-7257. (b) Chatterjea, J. N.; Bhakta, C.; Srivastava, S.; Lal, S. *Ind. J. Chem.* **1975**, *13*, 889-892.
15. (a) Duthaler, R. O.; Wegman, U. H. V. *Helv. Chim. Acta* **1984**, *67*, 1755-1766; (b) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927-3930.
16. Wells, G.; Berry, J. M.; Bradshaw, I. D.; Burger, A. M.; Seaton, A.; Wang, B.; Westwell, A. D.; Stevens, M. F. G. *J. Med. Chem.* **2003**, *46*, 532-541.

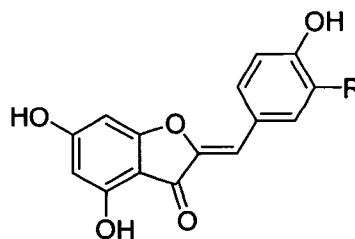
CHAPTER 4. GENERAL SYNTHESIS OF FLAVONES, AURONES, AND ACYL PHLOROGLUCINOLS

Introduction

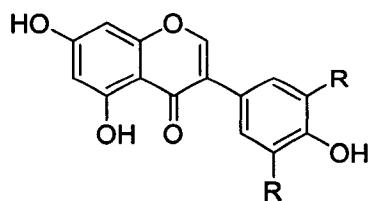
Plant derived natural products are increasingly being investigated as leads for pharmaceutical development. Using bioactivity-guided fractionation of plants reported to be useful as folk medicines, valuable bioactive compounds have been discovered. In recent years, new plant derived pharmaceuticals include Taxotere, Camptosar and teniposide.¹ As part of a multidisciplinary effort to identify new antiviral agents from *Echinacea* and *Hypericum*, we required a flexible synthetic route to oxygenated heterocycles, such as flavones, aurones, and acyl phloroglucinols.



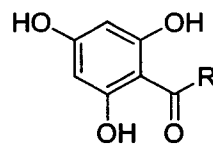
Flavones



Aurones



Isoflavones



Acyl phloroglucinols

Flavonoids are a group of naturally occurring polyphenolic compounds that are ubiquitously distributed in foods of plant origin.² More than 4000 flavonoids have been identified³ and can be divided into many subgroups of monomeric structures. Besides flavones, aurones, and isoflavones, other flavonoid subgroups include flavanones, flavonols, catechins, and anthocyanidins. (See Figure 1)

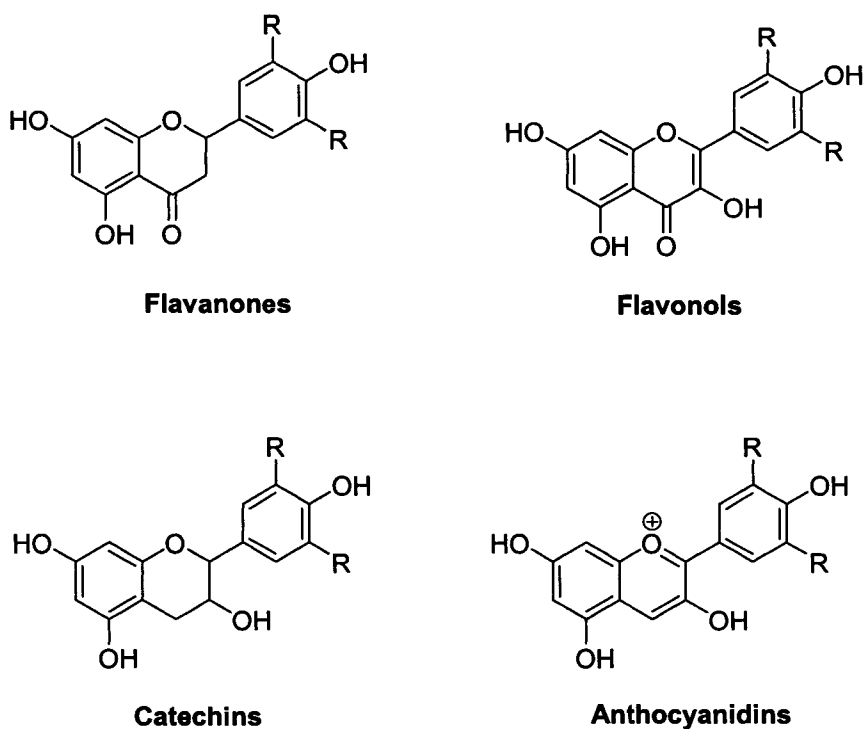


Figure 1. Other subgroups of flavonoids.

Variations in the heterocyclic ring C give rise to the subgroups of flavonoids. The high diversity of individual polyphenols within each of the subgroups derives mainly from the number and configuration of hydroxyl groups, and the multitude of substitution patterns in rings A and B.

A multitude of *in vitro* studies has shown that flavonoids can inhibit, and sometimes induce, a large variety of mammalian enzyme systems.⁴ Some of these enzymes are involved in important pathways that regulate cell division and proliferation, platelet aggregation, detoxification, and inflammatory and immune response. Thus, it is not surprising that effects of flavonoids have been found on various stages in the cancer process, on the immune system, and on haemostasis in cell systems and animals.⁴

Flavonoids inhibit cancer, cardiovascular diseases, such as coronary heart disease and atherosclerosis, inflammation, and other diseases in which an increase in oxidative stress has been implicated.⁵ The ability of flavonoids to act as classical electron or hydrogen donating antioxidants *in vivo* has been extensively reported and explain their protective effects against oxidative stress.⁵ The biosynthetic relationships among the main classes of flavonoids are presented in Figure 3, along with the enzymes.^{6,7}

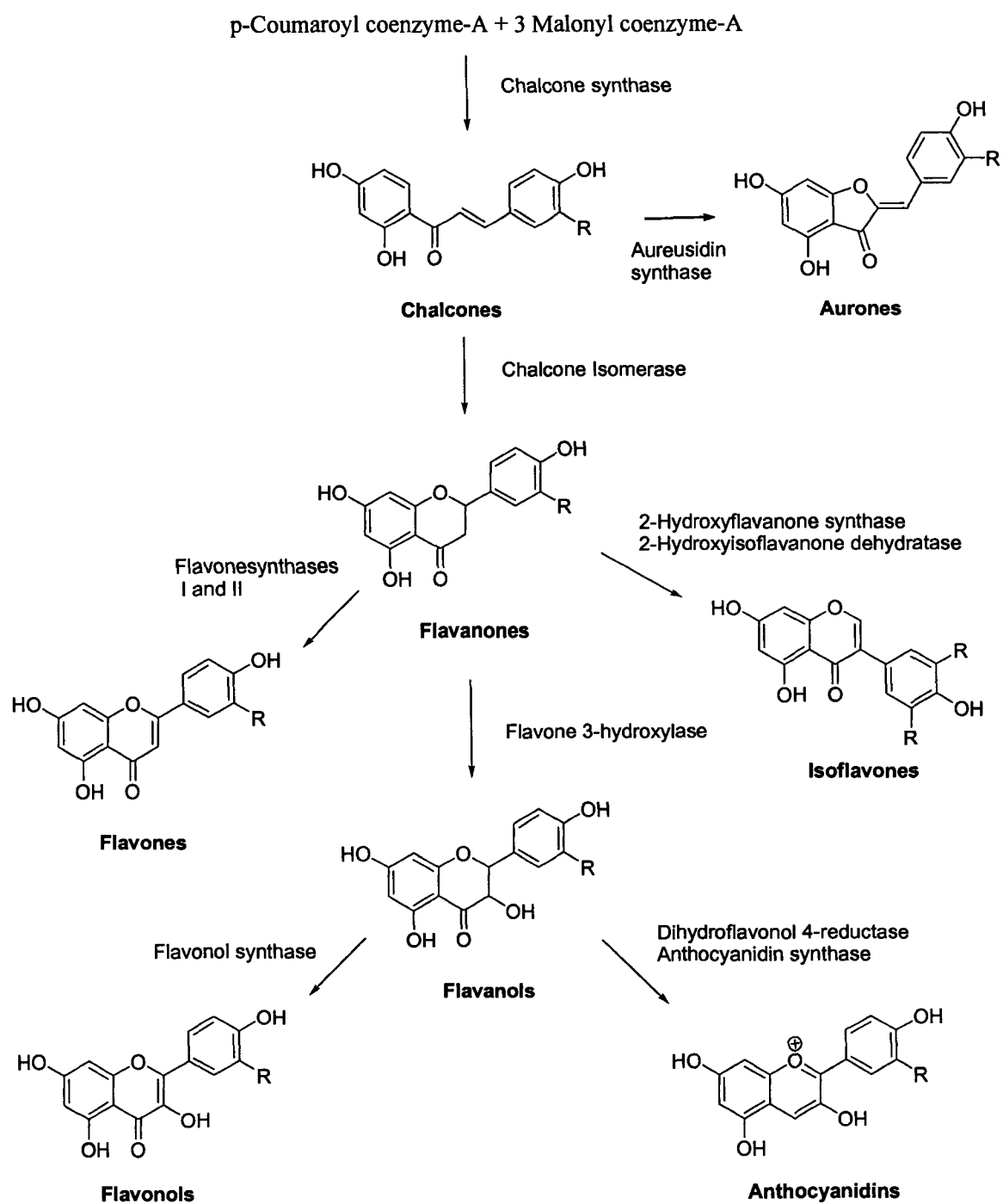


Figure 2. Major steps in flavonoids biosynthesis.

Acyl phloroglucinols and substituted acyl phloroglucinols are also a group of naturally occurring polyphenol-enriched products. Multifidol and multifidol glucoside isolated from the latex of *Jatropha multifida* (Euphorbiaceae)⁸ and hops (*Humulus lupulus* L, Cannabinaceae) have anti-inflammatory activity and were identified as novel inhibitors of COX-1.⁹ Acyl phloroglucinol (I) was isolated from *Hypericum foliosum* and was evaluated against a panel of multidrug-resistant strains of *Staphylococcus aureus*. Minimum inhibitory values ranged from 16 to 32 $\mu\text{g/mL}$.¹⁰

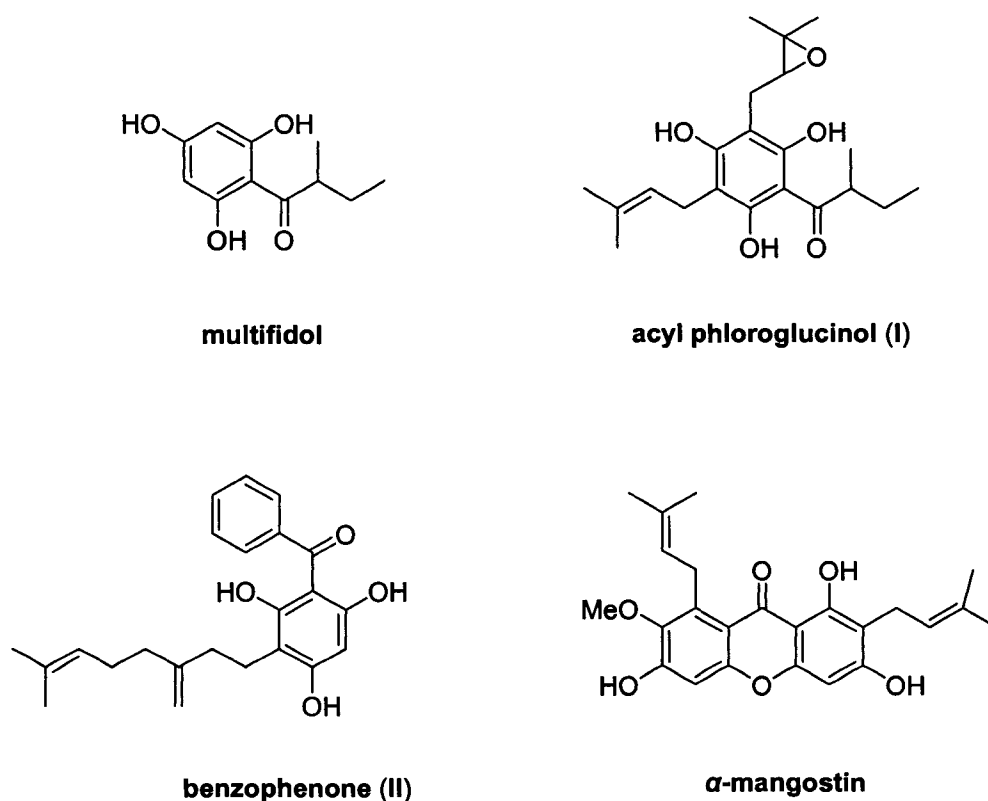
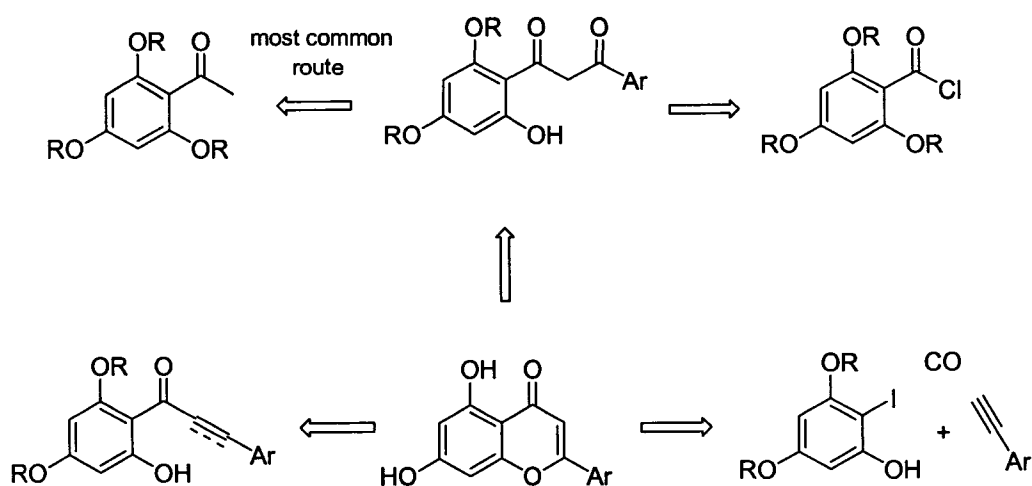


Figure 3. Acyl phloroglucinols

Benzophenone (II) and three other new benzophenones were isolated from *Tovomita longifolia* leaves.¹¹ Benzophenone (II) demonstrated cytotoxic activities against breast

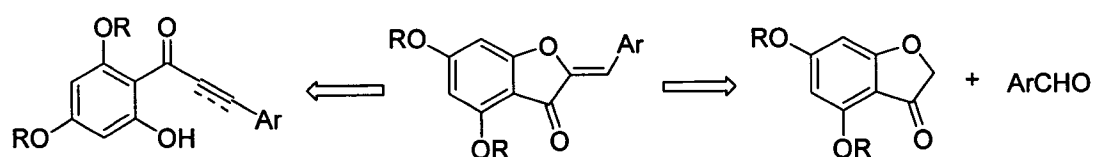
(MCF-7), central nervous system (SF-268), and lung (H-460) human cancer cell lines, while other compounds showed antimicrobial activity against *Klebsiella pneumoniae*, *Mycobacterium smegmatis*, *Pseudomonas aeruginosa*, *Salmonella gallinarum*, and *Staphylococcus aureus*.¹¹ α -Mangostin is known as a component of mangosteen *Garcinia mangostana* L. (Guttiferae). It was confirmed as a competitive antagonist of the histamine H1 receptor and an inhibitor of topoisomerases I and II. It showed antibacterial activity against *Helicobacter pylori* and inhibited oxidative damage due to human LDL.¹²

Many syntheses of flavones have been reported.¹³ All of the syntheses involved the C ring construction. The most common route to make the C ring is using acetophenones as starting materials to prepare diketone intermediates which undergo condensation to achieve flavones.¹³ The diketone intermediates can also be prepared from acyl chloride starting materials.¹⁴ Intramolecular unsaturated ketones¹⁵ and alkynyl ketones¹⁶ are also common intermediates in flavone synthesis. The recently developed route involves palladium coupling of an iodophenol with an alkyne followed by CO insertion.¹⁷

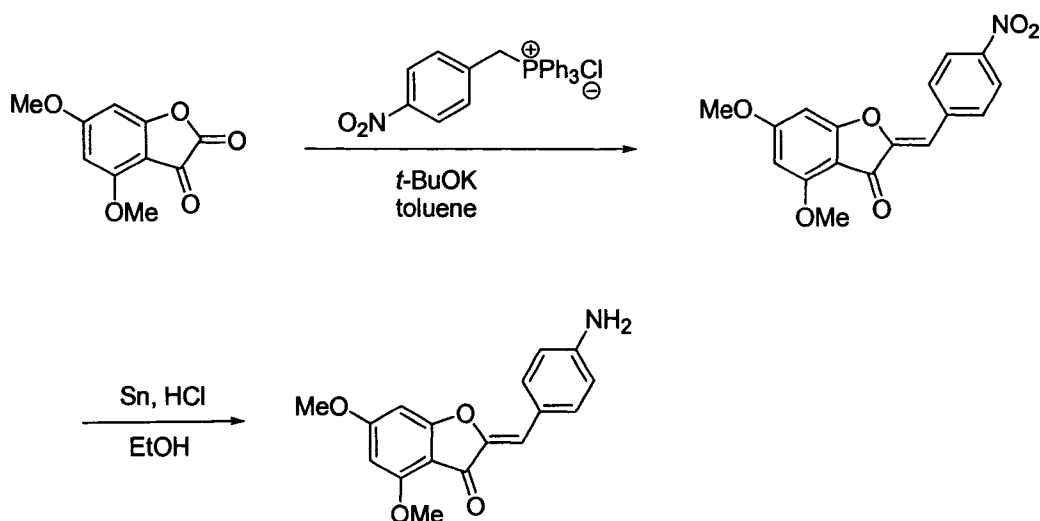


Aurones are less common than flavones and are thought to arise from chalcones by aureusidin synthase, a homolog of plant polyphenol oxidases.¹⁸ Several aurones show in vitro activity against *Cryptosporidium parvum* and *Plasmodium falciparum*.¹⁹ A number of 4,6-dioxyaurones show high-affinity binding to the cytosolic domain of P-glycoprotein and inhibit respiratory functions of mitochondria of *Leishmania* parasites.²⁰

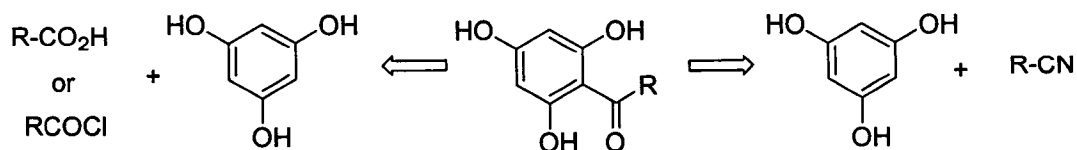
Aurones are synthesized by two main methods. One is the oxidative cyclization of 2'-hydroxychalcones²¹ or the cyclization of alkynyl ketones.¹⁶ The other one is the condensation of benzofuran-3(2H)-one with benzaldehyde.²² The key benzofuran-3(2H)-one is obtained through Friedel-Crafts acylation of phenol derivatives with a bromoacetonitrile.



Recently, our group has succeeded in a novel one-step approach to aurones. A Wittig reaction of 4,6-dimethoxybenzofuran-2,3-dione and 4-nitrobenzyltriphenylphosphite affords an aurone in one step. The nitro group is reduced by tin to give an amino aurone.

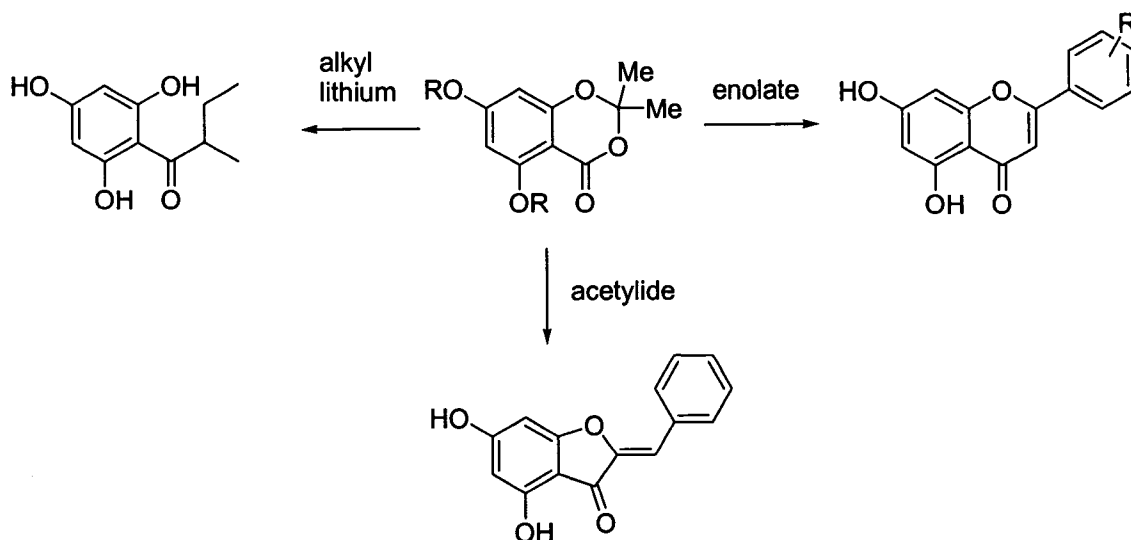


Acyl phloroglucinols are a diverse class of natural products that exhibit antibacterial activity, anticancer activity and antitubercular activity.⁸⁻¹⁰ They are broadly distributed among plant families. Several species of *Hypericum* contain biologically active acyl phloroglucinols.¹⁰ Interestingly, relatively few synthetic routes to these compounds have been reported. Acid-mediated addition of nitriles to phloroglucinols²³ and Lewis acid-mediated addition of nitriles to phloroglucinols²⁴ afforded acyl phloroglucinols. Also, acyl phloroglucinols have been made by Friedel-Crafts reactions with phloroglucinols.^{25, 26}

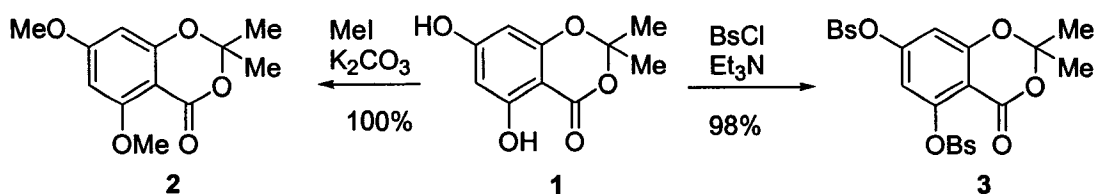


Results and Discussion

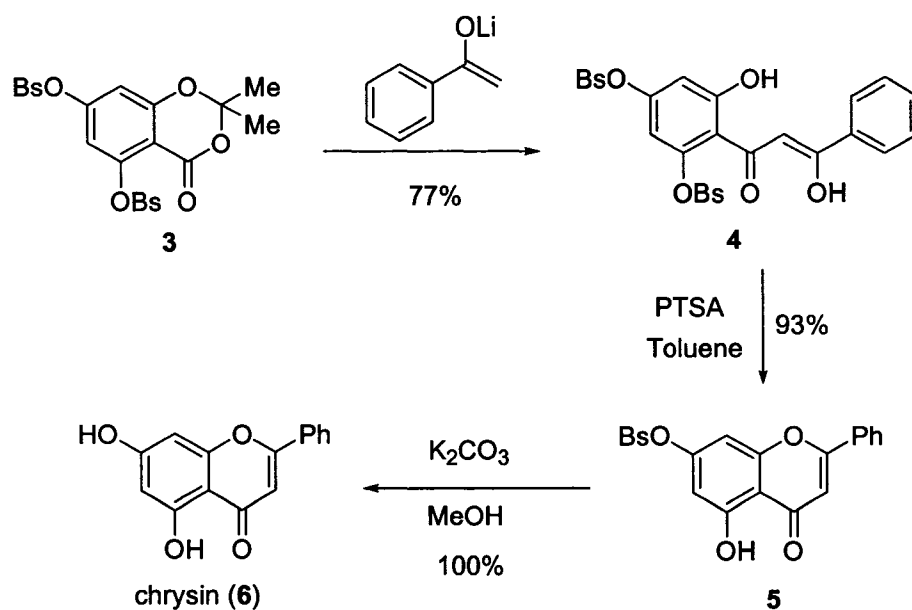
Although well-established synthetic routes to individual flavones, aurones, and acyl phloroglucinols have been communicated, no synthesis of all three classes of natural products via a common intermediate has been reported. We describe herein the use of 1,3-benzodioxin-4-ones, such as **2** and **3**, as direct precursors to flavones, aurones, and acyl phloroglucinols.



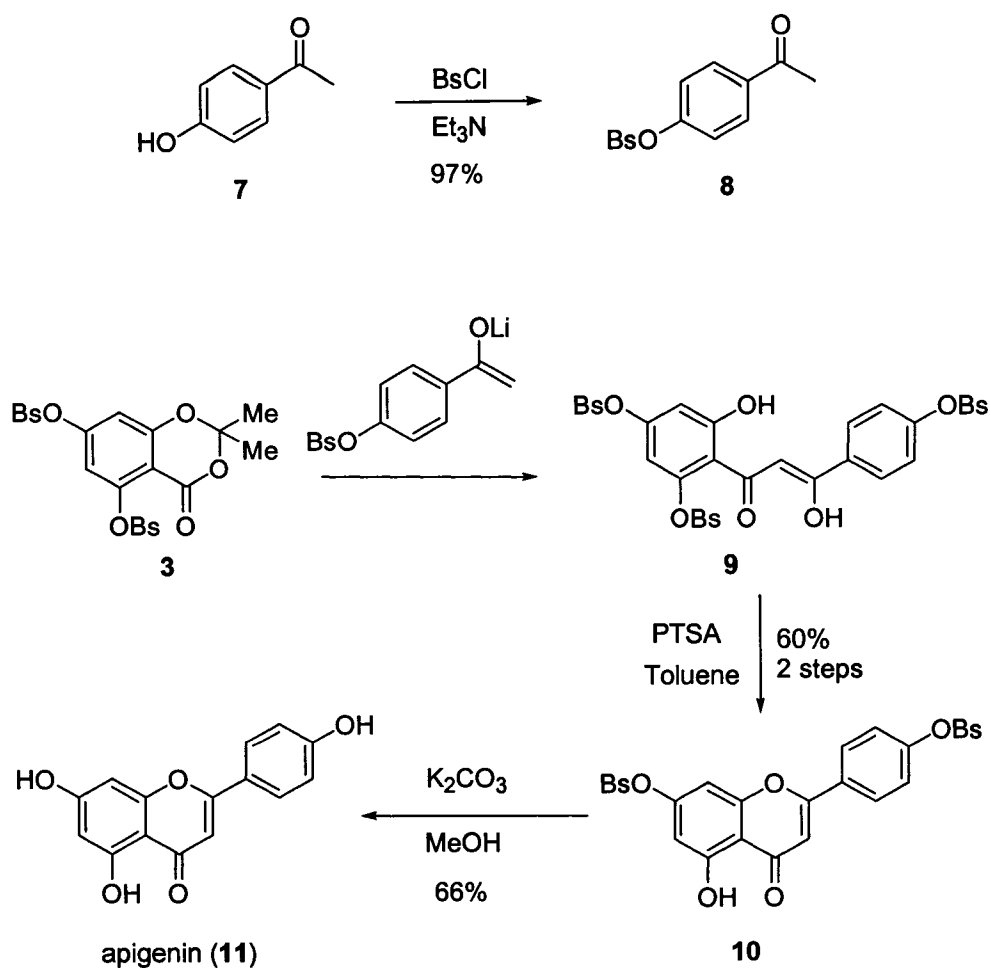
Recently, Takahashi reported an improved synthesis of **1**,²⁷ wherein 1,3,5-trihydroxybenzoic acid was reacted with acetone and thionyl chloride to provide **1** in 56% yield.²⁸ Methylation using methyl iodide and potassium carbonate afforded 1,3-benzodioxin-4-one **2** in 100% yield. Benzenesulfonylation of **1** using benzenesulfonyl chloride and triethylamine generated 1,3-benzodioxin-4-one **3** in 98% yield.



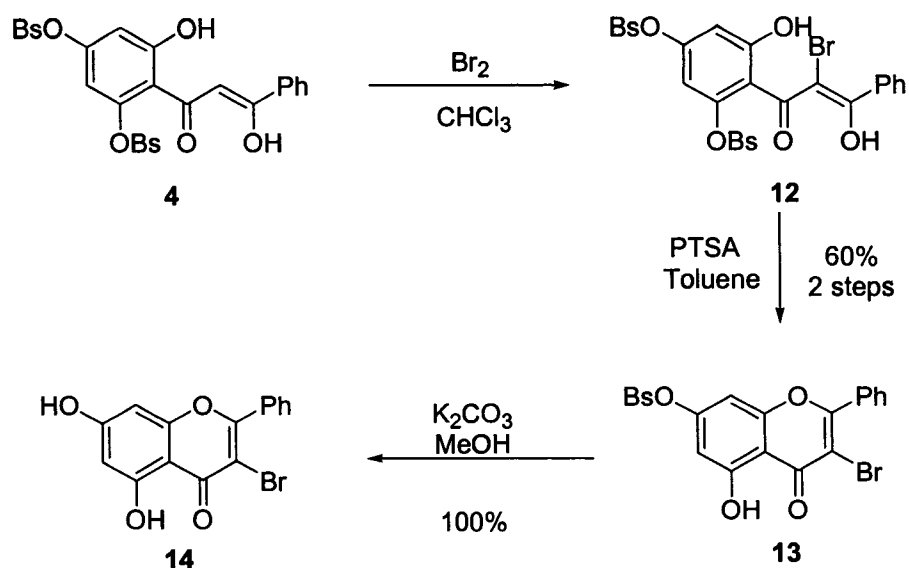
The nucleophilic addition chemistry of 1,3-benzodioxin-4-ones has not been studied extensively. The reaction of acetophenone enolate (prepared by deprotonation with lithium diisopropylamide) with **2** from $-78\text{ }^{\circ}\text{C}$ to $0\text{ }^{\circ}\text{C}$ returned starting materials. Fortunately, reaction of acetophenone enolate with the more electrophilic compound **3** generated β -diketone **4**. This could be cyclized using PTSA. During the cyclization, the *ortho*-benzenesulfonyloxy group was selectively deprotected. Then the remaining benzenesulfonyloxy group was deprotected using potassium carbonate in methanol to afford the natural product chrysin (**6**) in 72% overall yield. The proton and ¹³C NMR of our synthetic material were identical to the spectra obtained from an authentic sample of chrysin.



This methodology was then applied to a synthesis of apigenin (**11**). Apigenin, a component of *Matricaria recutita* flowers, is a central benzodiazepine receptors-ligand with anxiolytic effects.²⁹ Unexpectedly, the reaction of the *para*-methoxyacetophenone enolate with **3** returned starting materials. Fortunately, the LDA-derived enolate of *para*-(benzenesulfonyloxy)acetophenone reacted efficiently with **3** to produce the *beta*-diketone, which could be cyclized to give flavone **9** in 60% overall yield, followed by deprotection to provide apigenin (**11**) in 66% yield. Again, the proton and ¹³C NMR spectra of our synthetic material matched the spectra of an authentic sample.

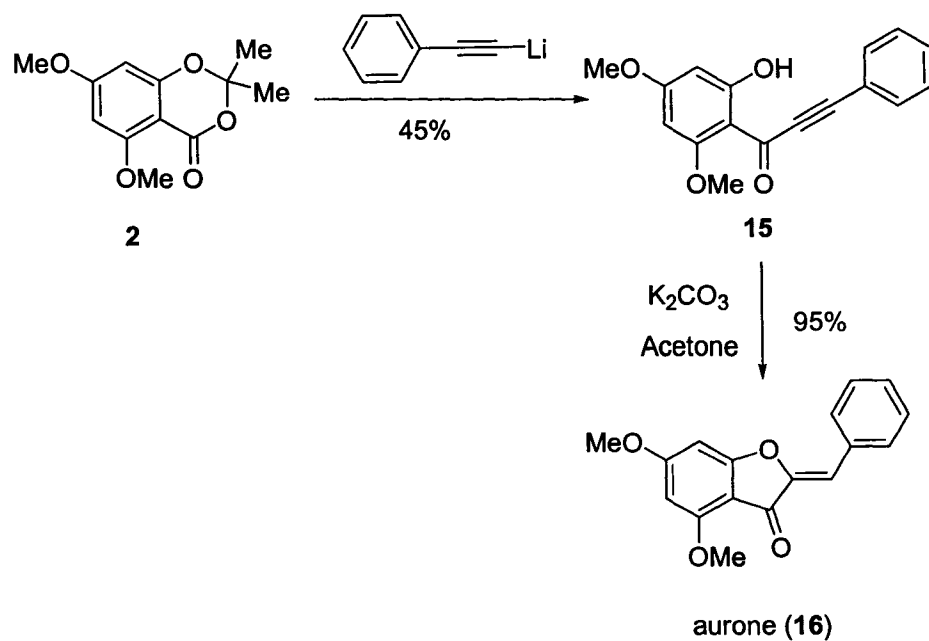


The scope of the work could be extended by reacting the anion of the diketone with electrophiles. For example, bromination of **4** produced bromo diketone **10**, which could be cyclized and deprotected to generate bromoflavone **12** in 60% overall yield. With a bromine at C-3 of chrysin, further chemistry, such as metal halogen exchange or palladium cross coupling would be easily carried out to provide other functionalized flavones.

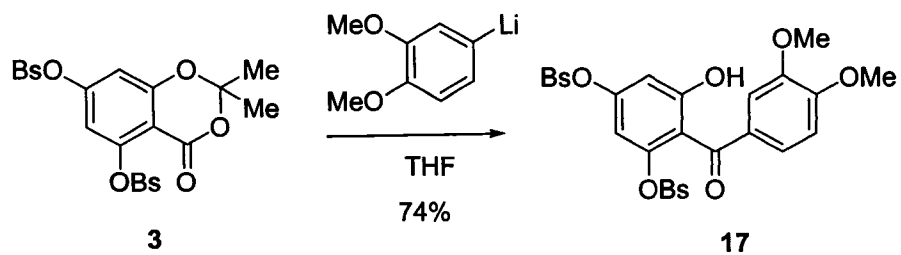


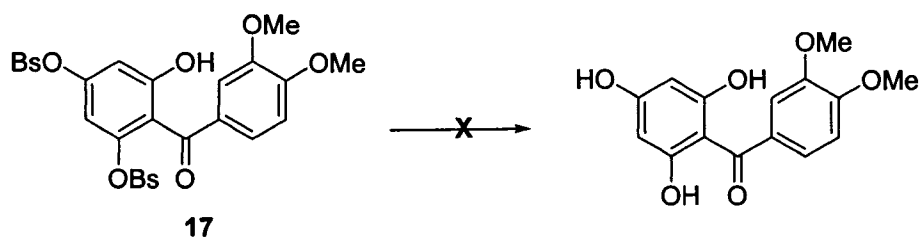
Aurones are less common than flavones. The most common synthetic route to aurones involves the condensation of aromatic aldehydes with 2,3-dihydrobenzofuran-3-ones.²² Our route to aurones is shown below. Treatment of 1,3-benzodioxin-4-one **2** with the lithium anion of phenylacetylene from -78°C to room temperature generated the acetylenic ketone in a 45% yield. The addition of excess lithium anion did not improve the yield of the ketone. In fact, the ketone product was converted into a tertiary alcohol when excess anion was applied. Although the acetylenic ketone was stable to the mildly basic workup conditions, this ketone rapidly cyclized to aurone **16** upon reaction with potassium

carbonate in acetone. The exclusive 5-exo reaction pathway has precedent in the work of Garcia.¹⁶ Herein, aurone was the kinetic product of 5-exo-dig ring closure, instead of the thermodynamic product of 6-endo-dig ring closure.

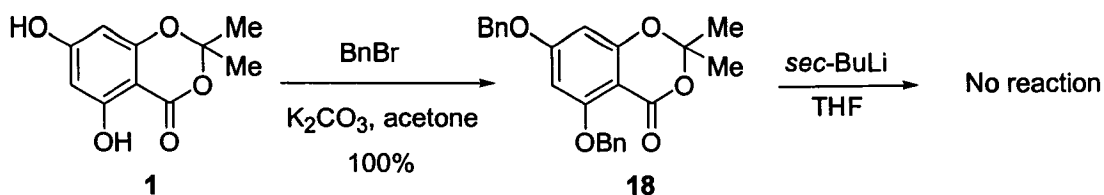


The general intermediate 3 was also applied to the synthesis of acyl phloroglucinols. The diphenylketone 17 was made by the reaction of 3 with 3,4-dimethoxyphenyl lithium.

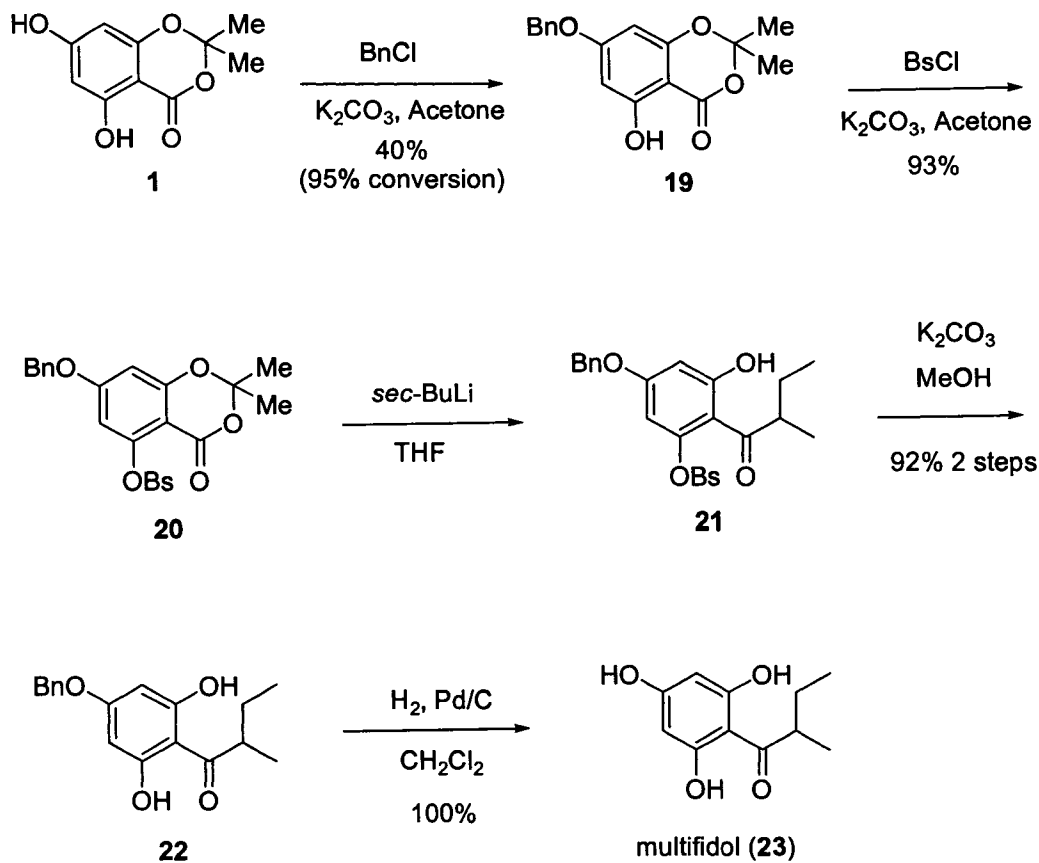




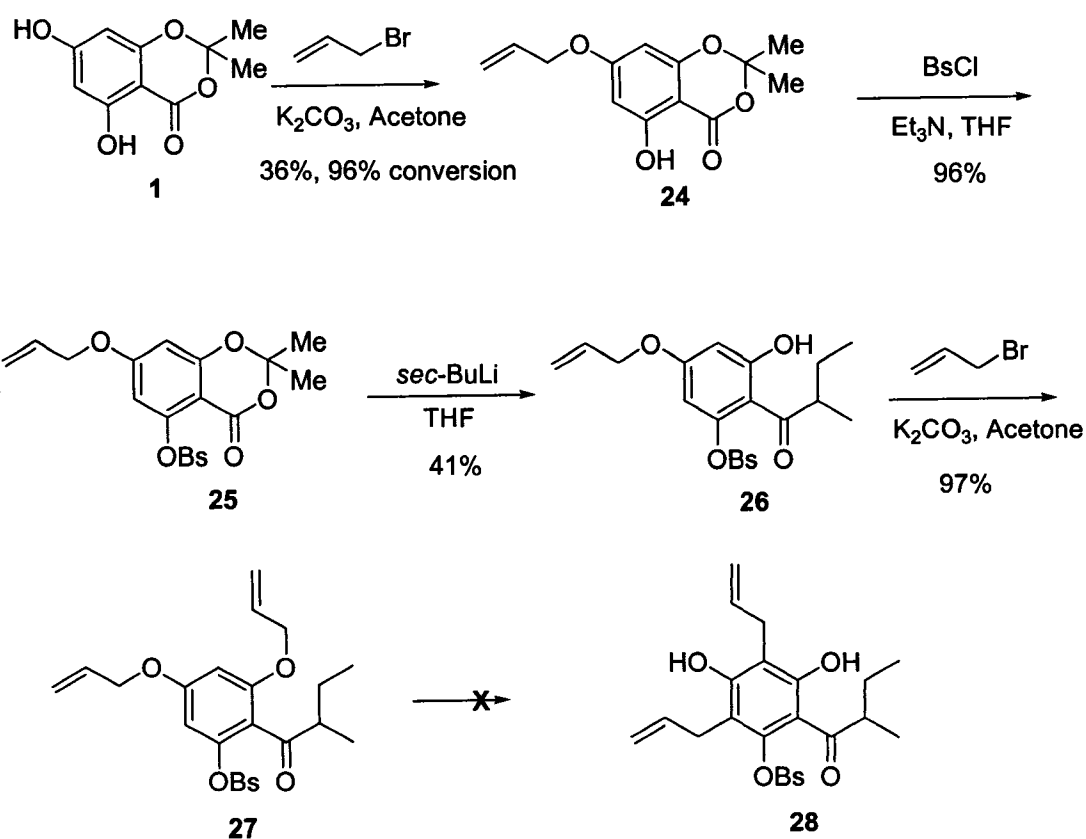
Unfortunately, in these acyl phloroglucinol systems, the *para*-benzenesulfonyloxy group was surprisingly stable. All attempts to deprotect both benzenesulfonyloxy groups failed using PTSA in toluene, K_2CO_3 in methanol, or even $Mg(OMe)_2$ in methanol. Benzyl protected 1,3-benzodioxin-4-one **18** was prepared to synthesize multifidol. However, the reaction of *sec*-BuLi with **18** returned only starting materials.



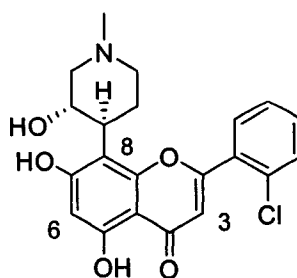
In order to succeed in multifidol synthesis, 1,3-benzodioxin-4-one **1** was protected using two different protecting groups. Product **20** underwent an addition reaction to generate *sec*-butyl ketone **21**. The *ortho*-benzenesulfonyloxy group was removed by K_2CO_3 in methanol and the *para*-benzyl group was deprotected by Pd/C hydrogenation in quantitative yield to achieve multifidol (**23**).



In order to synthesize diallyl-substituted acyl phloroglucinols, the *para*-hydroxyl group of 1 was first protected by allyl bromide, the *ortho*-hydroxyl group was protected as a benzenesulfonyloxy group to afford compound 25, which reacted with *sec*-BuLi to generate substituted acyl phloroglucinol 26. The free hydroxyl of 26 was then protected by an allyl group to give the diallyl protected acyl phloroglucinol 27. Unfortunately, the double Claisen rearrangement did not occur under either thermal conditions or microwave conditions. All the reactions returned only starting materials.

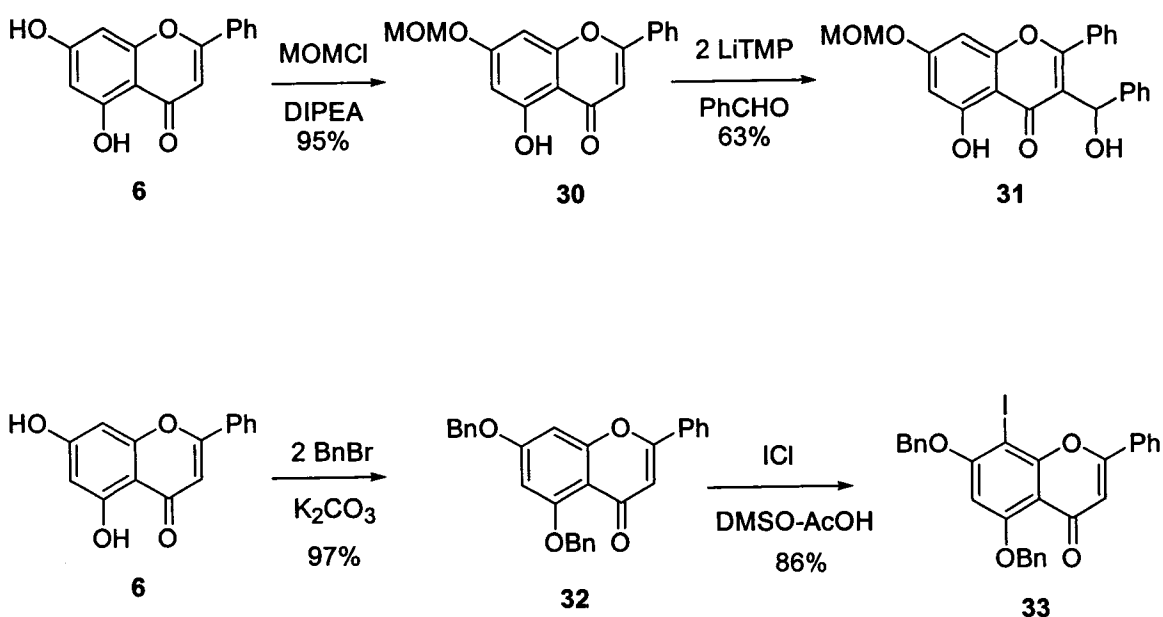


Flavopyridol **29** is a novel synthetic compound that has been shown to inhibit cyclin-dependent kinases causing cell cycle arrest and growth inhibition.³⁰ It is a promising anticancer agent with a novel mode of action.³¹ Our approach to the synthesis of analogs of **29** was to modify the known dibenzyl ether of readily available chrysin.



flavopyridol (**29**)

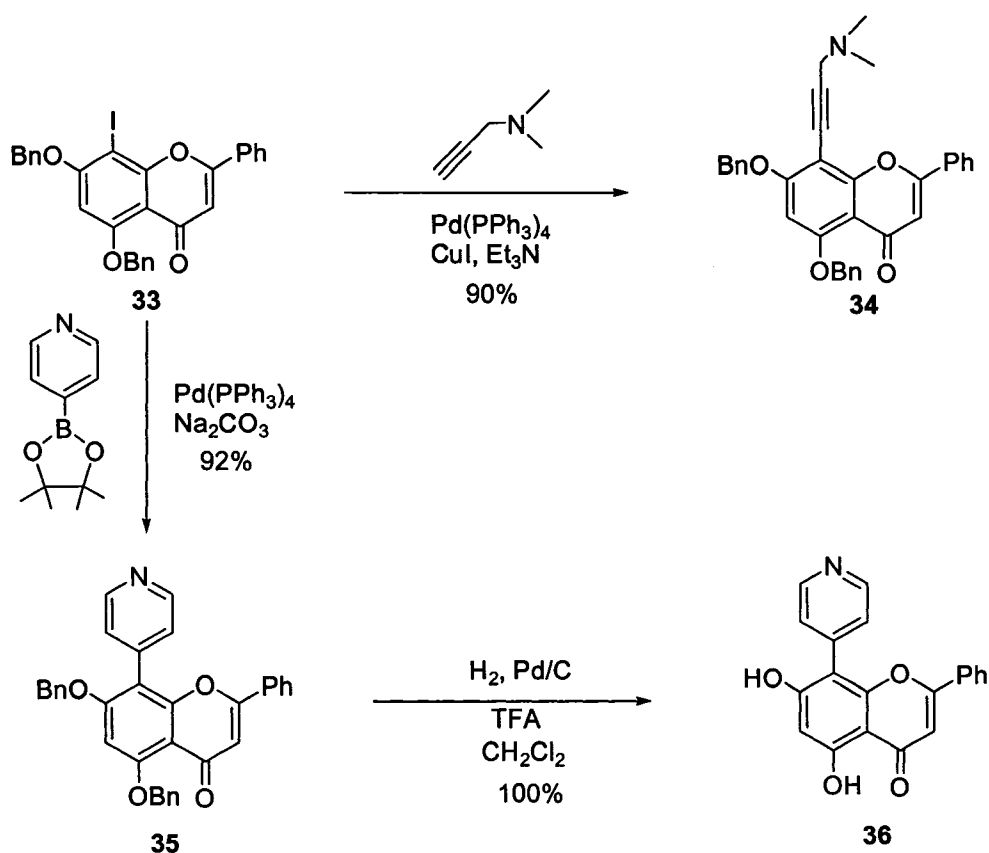
Although the synthesis of flavones have been widely studied, the regiochemical functionalization of flavones have not been systematically explored. Besides our 3-bromochrysin synthesis, C-3 of chrysin had been deprotonated directly by LiTMP (Lithium 2,2,6,6-tetramethylpiperidide) when the 7-hydroxyl group was protected with a MOM group.³² The dianion was quenched with benzaldehyde to give flavone **31**. Dibenzyl chrysin ether can be iodinated selectively at C-8 using iodine monochloride in DMSO and AcOH at 0 °C to give 8-iodoflavone **33**. The iodine at C-8 provided a great opportunity for further functionalization to synthesize flavopyridol analogs.



From iodo flavone **33**, palladium-mediated Sonogashira coupling with commercially available *N,N*-dimethylpropargylamine provided substituted flavone **34** in 90% yield. Palladium-mediated Suzuki-style coupling with commercially available 4-pyridineboronic

ester followed by hydrogenation in acidic media, afforded analog **36** in 92% yield from **33**.

The biological activity of flavopyridol analog **36** is in progress. More analogs could be synthesized from **33** depending on the biological results.



In conclusion, 1,3-benzodioxin-4-ones have been applied to the synthesis of flavones, aurones, and acyl phloroglucinols. Regiochemistry at C-3 and C-8 of flavone compounds has been studied. Regioselectively functionalized flavones have been synthesized for biological study. Further flavone analogs and natural products could be easily achieved.

Experimental Section

Unless stated otherwise, reactions were performed in flame-dried glassware under an argon atmosphere, using freshly distilled solvents. Diethyl ether (Et₂O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methylene chloride (CH₂Cl₂), benzene, toluene and diisopropylamine (*i*-Pr₂NH) were distilled from calcium hydride. *N,N*-Dimethyl formamide (DMF), dimethyl sulfoxide (DMSO), and hexamethylphosphoramide (HMPA) were distilled from calcium hydride and stored with activated 4 Å molecular sieves in sealed containers.

Unless stated otherwise, all reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) plates purchased from Aldrich (Cat. No. Z122785-25EA). Column or flash chromatography (silica) was performed with the indicated solvents using standard grade silica gel (particle size 230-400 mesh, 60 Å).

¹H and ¹³C NMR spectra were obtained on either a Varian 300 MHz or a Bruker 400 MHz spectrometer. Chemical shifts are reported relative to internal Me₄Si (¹H and ¹³C, δ 0.00 ppm) or chloroform (¹H, δ 7.26 ppm; ¹³C, δ 77.0 ppm). All melting points were obtained on a MEL-TEMP II variable temperature melting point apparatus from Laboratory Devices and are uncorrected. High-resolution mass spectra were recorded on a Kratos model MS-50 spectrometer, and low-resolution mass spectra were recorded on a Finnegan 4023 mass spectrometer.

5,7-Dimethoxy-2,2-dimethylbenzo[1,3]dioxin-4-one (2)

To 1,3-benzodioxin-4-one (1) (0.3 g, 1.43 mmol) and anhydrous K₂CO₃ (1.18 g, 8.57 mmol) in 40 mL of acetone at 0 °C was slowly added MeI (1.22 g, 8.57 mmol). The mixture

was warmed slowly to room temperature. The solution was extracted by H₂O and ethyl acetate (20 mL × 2). The organic layers were washed with brine and dried with MgSO₄. Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 2:1) afforded compound **2** (0.34 g, 100% yield) as a light yellow solid: m.p. 128-129 °C; ¹H NMR (300 MHz, CDCl₃) δ 1.68 (s, 6H), 3.83 (s, 3H), 3.91 (s, 3H), 6.06 (d, *J* = 3 Hz, 1H), 6.13 (d, *J* = 3 Hz, 1H). TLC (ethyl acetate: hexane = 1:1) R_f = 0.38.

5,7-Dibenzenesulfonyloxy-2,2-dimethylbenzo[1,3]dioxin-4-one (3)

To 1,3-benzodioxin-4-one (**1**) (0.24 g, 1.14 mmol) in 20 mL of THF at 0 °C was added Et₃N (0.25 g, 2.5 mmol), followed with slow addition of benzenesulfonyl chloride (0.44 g, 2.5 mmol). The mixture was warmed slowly to room temperature and stirred overnight. The solution was neutralized by 0.5M aqueous AcOH and extracted by H₂O and ethyl acetate (20 mL × 2). The organic layers were washed with brine and dried with MgSO₄. Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 2:1) afforded compound **3** (0.55 g, 98% yield) as a white solid: m.p. 132-133 °C; ¹H NMR (300 MHz, CDCl₃) δ 1.61 (s, 6H), 6.68 (d, *J* = 2.4 Hz, 1H), 6.75 (d, *J* = 2.4 Hz, 1H), 7.52-7.63 (m, 4H), 7.66-7.77 (m, 2H), 7.87-7.90 (m, 2H), 9.95-7.98 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 25.6, 106.8, 107.4, 110.6, 112.7, 128.6, 129.2, 129.4, 129.9, 134.8, 135.0, 135.3, 149.7, 154.4, 156.0, 158.1; MS *m/z* 490, 489, 432, 431, 141, 140, 77, 76; HRMS *m/z* for C₂₂H₁₈O₉S₂ calcd. 490.0392, measured. 490.0398. TLC (ethyl acetate: hexane = 1:2) R_f = 0.18.

3-Hydroxy-1-(2-hydroxy-4,6-dibenzenesulfonyloxyphenyl)-3-phenylpropenone (4)

To $i\text{Pr}_2\text{NH}$ (0.212 g, 2.1 mmol) in 10 mL of THF at $-78\text{ }^\circ\text{C}$ was added $n\text{-BuLi}$ (2.5M, 0.84 mL, 2.1 mmol) slowly. After 5 minutes, the temperature was increased to $0\text{ }^\circ\text{C}$ for 15 minutes. After the LDA solution was cooled to $-78\text{ }^\circ\text{C}$ again, acetophenone (0.30 g, 2.5 mmol) was added slowly. After stirring at $-78\text{ }^\circ\text{C}$ for 1 h, compound **3** (0.35 g, 0.71 mmol) in 5 mL of THF was added slowly. The mixture was warmed up slowly to room temperature and stirred 2 h. The solution was neutralized by 0.5M aqueous AcOH and extracted by H_2O and ethyl acetate ($20\text{ mL} \times 2$). The organic layers were washed with brine and dried with MgSO_4 . Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 2:1) afforded compound **4** (0.30 g, 77% yield) as a yellow solid. ^1H NMR (300 MHz, CDCl_3) δ 6.50 (d, $J = 2.4\text{ Hz}$, 1H), 6.55 (d, $J = 2.4\text{ Hz}$, 1H), 6.95 (s, 1H), 7.39-7.51 (m, 4H), 7.55-7.72 (m, 6H), 7.87-7.91 (m, 4H), 11.82 (s, OH); ^{13}C NMR (75 MHz, CDCl_3) δ 98.7, 109.2, 111.0, 114.1, 127.4, 128.7, 128.9, 129.2, 129.5, 129.7, 133.2, 133.3, 134.3, 135.0, 135.1, 135.2, 149.0, 153.0, 163.3, 179.5, 191.8; MS m/z 552, 470, 419, 394, 393, 103, 77. HRMS m/z for $\text{C}_{27}\text{H}_{20}\text{O}_9\text{S}_2$ calcd. 552.0549, measured. 552.0555. TLC (ethyl acetate: hexane = 1:2) R_f = 0.38.

5-Hydroxy-7-benzenesulfonyloxy-2-phenylchromen-4-one (**5**)

To compound **4** (0.3 g, 0.54 mmol) in 20 mL of toluene was added PTSA monohydrate (0.3 g, 1.6 mmol). The solution was heated to $114\text{ }^\circ\text{C}$ overnight. After the mixture was cooled to room temperature, evaporation under vacuum removed toluene. The residue was extracted by H_2O and ethyl acetate ($20\text{ mL} \times 2$). The organic layers were washed with brine and dried with MgSO_4 . Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 4:1) afforded compound **5** (0.20 g, 90% yield). ^1H

NMR (300 MHz, CDCl_3) δ 6.34 (d, $J = 2.1$ Hz, 1H), 6.74 (d, $J = 1.5$ Hz, 1H), 6.90 (d, $J = 2.1$ Hz, 1H), 7.53-7.61 (m, 5H), 7.69-7.73 (m, 1H), 7.86-7.93 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 101.9, 105.9, 106.4, 109.8, 126.7, 128.6, 129.5, 129.7, 130.8, 132.6, 135.0, 135.3, 154.4, 156.8, 162.2, 165.2, 183.0; MS m/z 394, 393, 331, 329, 301, 288, 151, 141, 123, 122, 121, 101, 77, 76, 75; HRMS m/z for $\text{C}_{21}\text{H}_{14}\text{O}_6\text{S}$ calcd. 394.0511, measured. 394.0516. TLC (ethyl acetate: hexane = 1:2) $R_f = 0.42$.

Chrysin (6)

To compound **5** (60 mg, 0.15 mmol) and anhydrous K_2CO_3 (0.5 g) was added 20 mL of methanol. The mixture was heated to 66 °C for 2 h. After the mixture was cooled to room temperature, concentrated HCl was added to neutralize the solution. The KCl salts were removed by filtration. The filtrate was evaporated under vacuum. The residue was dissolved by 20 mL of ethyl acetate, washed with saturated NaHCO_3 , brine, and dried with MgSO_4 . Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 4:1) afforded chrysin **6** (38 mg, 100% yield). ^1H NMR (300 MHz, CD_3COCD_3) δ 6.28 (d, $J = 2.1$ Hz, 1H), 6.58 (d, $J = 2.1$ Hz, 1H), 6.80 (s, 1H), 7.61 (m, 3H), 8.07 (m, 2H), 12.9 (s, OH); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 94.2, 99.2, 104.9, 105.5, 126.6, 129.3, 131.6, 132.1, 158.2, 162.7, 164.0, 164.4, 182.5. TLC (ethyl acetate: hexane = 1:2) $R_f = 0.25$.

4-Bezenesulfonyloxyacetophenone (8)

To 4-hydroxyacetophenone (1.36 g, 10 mmol) in 30 mL of THF at 0 °C was added Et_3N (1.5 g, 15 mmol), followed with benzenesulfonyl chloride (2.47 g, 14 mmol). The mixture was warmed slowly to room temperature and stirred for 2 h. The solution was

extracted by H₂O and ethyl acetate (20 mL × 2). The organic layers were washed with brine and dried with MgSO₄. Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 6:1 and 2:1) afforded compound **8** (0.27 g, 97% yield). ¹H NMR (300 MHz, CDCl₃) δ 2.57 (s, 3H), 7.08 (m, 2H), 7.54 (m, 2H), 7.69 (m, 1H), 7.82-7.91 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 26.8, 122.7, 128.6, 129.6, 130.3, 134.8, 135.3, 136.0, 153.1, 196.9; MS *m/z* 276, 261, 140, 84, 77, 75; HRMS *m/z* for C₁₄H₁₂O₄S calcd. 276.0456, measured. 276.0460. TLC (ethyl acetate: hexane = 1:2) R_f = 0.18.

3-Hydroxy-1-(2-hydroxy-4,6-dibenzenesulfonyloxyphenyl)-3-(4'-benzenesulfonyloxy)phenylpropenone (9)

To *i*-Pr₂NH (0.13 g, 1.3 mmol) in 5 mL of THF at -78 °C was added *n*-BuLi (2.5M, 0.52 mL, 1.3 mmol) slowly. After 5 minutes, the temperature was increased to 0 °C for 15 minutes. After the LDA solution was cooled to -78 °C again, compound **8** (0.36 g, 1.3 mmol) in 5 mL of THF was added slowly. After stirring at -78 °C for 1 h, compound **3** (0.25 g, 0.5 mmol) in 5 mL of THF was added slowly. The mixture was warmed slowly to room temperature and stirred for 2 h. The solution was neutralized by 0.5M aqueous AcOH and extracted by H₂O and ethyl acetate (20 mL × 2). The organic layers were washed with brine and dried with MgSO₄. Evaporation of the solvent afforded crude compound **9** (0.5 g), which was used directly for next step.

5-Hydroxy-7-benzensulfonyloxy-2-(4-benzenesulfonyloxyphenyl)chromen-4-one (10)

To crude compound **9** (0.25 g) in 10 mL of toluene was added PTSA monohydrate (0.15 g). The solution was heated to 114 °C overnight. After the mixture was cooled to

room temperature, evaporation under vacuum removed toluene. The residue was extracted by H₂O and ethyl acetate (20 mL × 2). The organic layers were washed with brine and dried with MgSO₄. Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 2:1) afforded compound **10** (0.16 g, 60% yield over 2 steps). ¹H NMR (300 MHz, CDCl₃) δ 6.35 (d, *J* = 2.1 Hz, 1H), 6.67 (s, 1H), 6.88 (d, *J* = 2.1 Hz, 1H), 7.18 (m, 2H), 7.51-7.61 (m, 5H), 7.68-7.74 (m, 2H), 7.81-7.92 (m, 5H), 12.63 (s, OH).

Apigenin (11)

To compound **10** (50 mg, 0.09 mmol) and anhydrous K₂CO₃ (0.5 g) was added 20 mL of methanol. The mixture was heated to 66 °C for 5 h. After the mixture was cooled to room temperature, concentrated HCl was added to neutralize the solution. The KCl salts were removed by filtration. The filtrate was evaporated under vacuum. The residue was recrystallized by 5 mL of MeOH and 2 mL of H₂O to afford apigenin **11** (16 mg, 66% yield). ¹H NMR (300 MHz, CD₃COCD₃) δ 6.25 (d, *J* = 2.1 Hz, 1H), 6.54 (d, *J* = 2.1 Hz, 1H), 6.64 (s, 1H), 7.02 (m, 2H), 7.96 (m, 2H), 13.03 (s, OH); ¹³C NMR (75 MHz, CD₃COCD₃) δ 94.1, 99.0, 103.4, 104.7, 116.2, 122.6, 128.6, 158.1, 161.2, 162.7, 164.2, 164.4, 182.4. TLC (ethyl acetate: hexane = 1:1) R_f = 0.20.

2-Bromo-3-hydroxy-1-(2-hydroxy-4,6-dibenzenesulfonyloxy -phenyl)-3-phenyl-propenone (12)

To compound **4** (0.178 g, 0.32 mmol) and NaOAc (53 mg, 0.64 mmol) in 10 mL of chloroform was added 0.5M bromine solution in acetic acid (0.64 mL, 0.32 mmol) at room temperature. After 10 minutes, the solution was extracted by H₂O and CH₂Cl₂ (10 mL × 2).

The organic layers were washed with brine and dried with MgSO_4 . Evaporation of the solvent provided crude compound **12** (0.2 g) which was used directly in the next step.

3-Bromo-5-hydroxy-7-benzensulfonyloxy-2-phenylchromen-4-one (13)

The crude compound **12** (0.2 g) in 20 mL of toluene was added PTSA monohydrate (50 mg). The solution was heated to 120 °C overnight. When the mixture was cooled to room temperature, evaporation under vacuum removed toluene. The residue was extracted by H_2O and ethyl acetate (20 mL \times 2). The organic layers were washed with brine and dried with MgSO_4 . Evaporation of solvent and purification by flash chromatography (hexane: ethyl acetate = 4:1) afforded compound **13** (90 mg, 60% yield over 2 steps). ^1H NMR (300 MHz, CDCl_3) δ 6.43 (d, J = 2.4 Hz, 1H), 6.84 (d, J = 2.4 Hz, 1H), 7.54-7.60 (m, 5H), 7.69-7.73 (m, 1H), 7.81-7.85 (m, 2H), 7.88-7.92 (m, 2H). TLC (ethyl acetate: hexane = 1:2) R_f = 0.56.

3-Bromochrysin (14)

To compound **13** (50 mg, 0.11 mmol) and anhydrous K_2CO_3 (0.5 g) was added 20 mL of methanol. The mixture was heated to 66 °C for 3 h. After the mixture was cooled to room temperature, concentrated HCl was added to neutralize the solution. The KCl salts were removed by filtration. The filtrate was evaporated under vacuum. The residue was dissolved by 20 mL of ethyl acetate, washed with saturated NaHCO_3 , brine, and dried with MgSO_4 . Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 4:1) afforded 3-bromochrysin **14** (36 mg, 100% yield). ^1H NMR (300 MHz, CD_3COCD_3) δ 6.36 (d, J = 2.1 Hz, 1H), 6.48 (d, J = 2.1 Hz, 1H), 7.63 (m, 3H), 7.90 (m, 2H), 12.46 (s, OH);

^{13}C NMR (75 MHz, CD_3COCD_3) δ 94.1, 99.6, 103.5, 106.2, 128.6, 129.5, 131.5, 133.0, 157.8, 162.2, 162.9, 164.9, 177.1; MS m/z 332, 253, 197, 152, 124, 91, 69, 44; HRMS m/z for $\text{C}_{15}\text{H}_9\text{BrO}_4$ calcd. 331.9684, measured. 331.9688. TLC (ethyl acetate: hexane = 1:2) R_f = 0.31.

1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-phenylpropynone (15)

To phenylacetylene (20 mg, 0.2 mmol) in 5 mL of THF at 0 °C was added *n*-BuLi (2.5 M, 80 μL , 0.2 mmol) slowly. After 1 hour at 0 °C, the lithium reagent was cooled to -78 °C, compound **2** (43 mg, 0.18 mmol) in 2 mL of THF was added slowly. The mixture was warmed slowly to room temperature and stirred for 2 h. The solution was neutralized by 0.5M aqueous AcOH, extracted by H_2O and ethyl acetate (20 mL \times 2). The organic layers were washed with brine and dried with MgSO_4 . Evaporation of the solvent and purification by flash chromatography twice (hexane: ethyl acetate = 2:1 and hexane: dichloromethane = 1:2) afforded starting material **2** (19 mg) and product **15** (23 mg, 45% yield, 82% conversion). ^1H NMR (300 MHz, CDCl_3) δ 3.85 (s, 3H), 3.93 (s, 3H), 5.94 (d, J = 2.4 Hz, 1H), 6.07 (d, J = 2.4 Hz, 1H), 7.42 (m, 3H), 7.63 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 55.9, 56.0, 89.9, 91.3, 93.7, 95.1, 107.3, 121.4, 128.8, 130.7, 133.2, 162.9, 167.6, 168.5, 177.8. TLC (dichloromethane: hexane = 2:1) R_f = 0.24.

2-Benzylidene-4,6-dimethoxybenzofuran-3-one (16)

To compound **15** (10 mg) and K_2CO_3 (10 mg) in a sealed tube was added 2 mL of acetone and heated to 56 °C for 6 h. After the solution was cooled to room temperature, it was neutralized by 0.5M aqueous AcOH and extracted by H_2O and ethyl acetate (5 mL \times 2).

The organic layers were washed with brine and dried with MgSO_4 . Evaporation of solvent and purification by flash chromatography twice (hexane: ethyl acetate = 2:1) afforded aurone **16** (9.5 mg, 95% yield) as a yellow solid: m.p 148-151 °C; ^1H NMR (300 MHz, CDCl_3) δ 3.93 (s, 1H), 3.97 (s, 1H), 6.15 (d, J = 1.8 Hz, 1H), 6.41 (d, J = 1.8 Hz, 1H), 6.79 (s, 1H), 7.44 (m, 3H), 7.88 (m, 2H).

(2,4-Dibenzenesulfonyloxy-6-hydroxyphenyl)-(3,4-dimethoxyphenyl)-methanone (17)

To 4-Bromoveratrole (0.26 g, 1.2 mmol) in 5 mL of THF at -78 °C was added $n\text{-BuLi}$ slowly. After 30 minutes at -78 °C, the temperature was increased to 0 °C for one more hour and was cooled to -78 °C. Compound **3** (0.147 g, 0.3 mmol) in 10 mL of THF was added slowly at -78 °C. The mixture was warmed slowly to room temperature and stirred overnight. The solution was neutralized by 0.5M aqueous HCl, extracted with H_2O and ethyl acetate (20 mL \times 2). The organic layers were washed with brine and dried with MgSO_4 . Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 2:1) afforded compound **17** (0.125 g, 74% yield). ^1H NMR (300 MHz, CDCl_3) δ 3.88 (s, 3H), 3.91 (s, 3H), 6.50 (d, J = 2.4 Hz, 1H), 6.67 (d, J = 2.4 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 7.11-7.17 (m, 2H), 7.40-7.42 (m, 4H), 7.56-7.64 (m, 3H), 7.69-7.73 (m, 1H), 7.88-7.91 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 56.27, 56.32, 109.4, 109.9, 110.7, 111.7, 115.8, 125.7, 128.4, 128.6, 129.3, 129.7, 130.7, 134.6, 134.8, 135.0, 135.2, 147.8, 148.9, 152.7, 154.1, 161.4, 194.5; MS m/z 570, 429, 287, 259, 164, 137, 77; HRMS m/z for $\text{C}_{27}\text{H}_{22}\text{O}_{10}\text{S}_2$ calcd. 570.0654, measured 570.0663. TLC (ethyl acetate: hexane = 1:1) R_f = 0.14.

5,7-Bis-benzyloxy-2,2-dimethylbenzo[1,3]dioxin-4-one (18)

To 1,3-benzodioxin-4-one (**1**) (0.3 g, 1.43 mmol) and anhydrous K_2CO_3 (1.18 g, 8.57 mmol) in 40 mL of acetone at 0 °C was slowly added BnBr (1.22 g, 7.15 mmol). The mixture was warmed slowly to room temperature and stirred overnight. The solution was extracted with H_2O and ethyl acetate (20 mL \times 2). The organic layers were washed with brine and dried with $MgSO_4$. Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 4:1) afforded compound **18** (0.56 g, 100% yield). 1H NMR (300 MHz, $CDCl_3$) δ 1.70 (s, 6H), 5.03 (s, 2H), 5.19 (s, 2H), 6.15 (d, J = 2.4 Hz, 1H), 6.27 (d, J = 2.4 Hz, 1H), 7.29-7.41 (m, 8H), 7.54 (m, 2H).

7-Benzoyloxy-5-hydroxy-2,2-dimethylbenzo[1,3]dioxin-4-one (**19**)

To 1,3-benzodioxin-4-one (**1**) (0.3 g, 1.43 mmol) and anhydrous K_2CO_3 (0.2 g, 1.43 mmol) in 20 mL of acetone at 0 °C was slowly added BnCl (0.18 g, 1.42 mmol). The mixture was warmed slowly to room temperature, and then heated to 60 °C overnight. After the solution was cooled to room temperature, it was extracted with H_2O and ethyl acetate (20 mL \times 2). The organic layers were washed with brine and dried with $MgSO_4$. Evaporation of solvent and purification by flash chromatography (hexane: ethyl acetate = 4:1) afforded starting material **1** (0.17 g) and compound **19** (0.17 g, 40% yield, 95% conversion). 1H NMR (300 MHz, $CDCl_3$) δ 1.72 (s, 6H), 5.05 (s, 2H), 6.08 (d, J = 2.1 Hz, 1H), 6.22 (d, J = 2.1 Hz, 1H), 7.40 (m, 5H), 10.47 (s, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 70.7, 93.5, 95.5, 96.8, 107.2, 127.8, 128.6, 129.0, 135.8, 157.1, 163.3, 165.4, 167.0; MS m/z 300, 241, 199, 122, 90; HRMS m/z for $C_{17}H_{16}O_5$ calcd. 300.0998, measured 300.1003. TLC (ethyl acetate: hexane = 1:2) R_f = 0.63.

7-Benzyloxy-5-benzenesulfonyloxy-2,2-dimethylbenzo[1,3]dioxin-4-one (20)

To compound **19** (0.33 g, 1.1 mmol) and anhydrous K_2CO_3 (0.6 g, 4.4 mmol) in 20 mL of acetone at room temperature was added benzenesulfonyl chloride (0.77 g, 4.4 mmol). The mixture was stirred at room temperature overnight. After vacuum evaporation, the residue was extracted by H_2O and ethyl acetate (20 mL \times 2). The organic layers were washed with brine and dried with $MgSO_4$. Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 4:1 to 2:1) afforded compound **20** (0.44 g, 93% yield). 1H NMR (300 MHz, $CDCl_3$) δ 1.58 (s, 6H), 5.06 (s, 2H), 6.45 (d, J = 2.1 Hz, 1H), 6.71 (d, J = 2.1 Hz, 1H), 7.40 (m, 5H), 7.52 (m, 2H), 7.65 (m, 1H), 8.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7, 71.1, 101.6, 101.8, 106.1, 106.7, 127.9, 128.9, 129.1, 129.2, 134.7, 135.2, 135.4, 150.2, 156.8, 158.8, 164.7; MS m/z 440, 382, 240, 172, 140, 89, 76; HRMS m/z for $C_{23}H_{20}O_7S$ calcd. 440.0930, measured 440.0938. TLC (ethyl acetate: hexane = 1:2) R_f = 0.26.

1-(4-Benzyloxy-2-hydroxy-6-benzensulfonyloxyphenyl)-2-methylbutan-1-one (21)

To compound **20** (0.1 g, 0.22 mmol) in 20 mL of THF at $-78^\circ C$ was slowly added *sec*-BuLi (1.27 M, 0.37 mL, 0.48 mmol). After 10 minutes at $-78^\circ C$, 0.1 mL of glacial AcOH was added. The mixture was warmed slowly to $0^\circ C$, and extracted with H_2O and ethyl acetate (20 mL \times 2). The organic layers were washed with brine, dried with $MgSO_4$. Evaporation of the solvent afforded crude **21**, which was used directly in the next step.

1-(4-Benzyloxy-2,6-dihydroxyphenyl)-2-methylbutan-1-one (22)

To crude **21** in 20 mL of methanol was added anhydrous K_2CO_3 (1.0 g). The mixture was heated to 50 °C overnight. After the solution was cooled to room temperature, 0.5 M AcOH was added to neutralize the solution. Evaporation removed most of the solvent. The residue was extracted with H_2O and ethyl acetate (20 mL \times 2). The organic layers were washed with brine and dried with MgSO_4 . Evaporation of solvent and purification by flash chromatography (hexane: ethyl acetate = 4:1) afforded compound **20** (63 mg, 92% yield over 2 steps). ^1H NMR (300 MHz, CDCl_3) δ 0.91 (t, J = 7.5 Hz, 3H), 1.16 (d, J = 6.6 Hz, 3H), 1.40 (m, 1H), 1.84 (m, 1H), 3.74 (m, 1H), 5.03 (s, 2H), 6.00 (s, 2H), 7.35 (m, 5H); MS m/z 300, 242, 90; HRMS m/z for $\text{C}_{18}\text{H}_{20}\text{O}_4$ calcd. 300.1362, measured 300.1365. TLC (ethyl acetate: hexane = 1:4) R_f = 0.29.

Multifidol (**23**)

The round bottom flask which contained compound **22** (9 mg, 0.03 mmol) and 3 mL of CH_2Cl_2 was evacuated by water aspirator until the solvent was bubbling and then flushed with H_2 gas. This operation was repeated three times before the Pd/C (10 mg) addition. After the Pd/C addition, this evacuation / H_2 gas flush was repeated three times. The mixture was stirred under H_2 gas at room temperature overnight. When the reaction was complete, the mixture was filtered through Celite and the filtrate was concentrated and purified by flash chromatography (hexane: ethyl acetate = 2:1) to afford compound **7** (7 mg, 100% yield). ^1H NMR (300 MHz, CD_3COCD_3) δ 0.89 (t, J = 8.2 Hz, 3H), 1.12 (d, J = 6.6 Hz, 3H), 1.37 (m, 1H), 1.82 (m, 1H), 3.85 (m, 1H), 5.93 (s, 2H); MS m/z 210, 152; HRMS m/z for $\text{C}_{11}\text{H}_{14}\text{O}_4$ calcd. 210.0892, measured 210.0896. TLC (ethyl acetate: hexane = 1:2) R_f = 0.24.

7-Allyloxy-5-hydroxy-2,2-dimethylbenzo[1,3]dioxin-4-one (24)

To 1,3-benzodioxin-4-one **1** (0.4 g, 1.9 mmol) and anhydrous K_2CO_3 (1.1 g, 8 mmol) in 20 mL of acetone at 0 °C was added allyl bromide (0.24 g, 2 mmol) slowly. The mixture was warmed slowly to room temperature and stirred for 8 h at room temperature. The solution was neutralized by 0.5 M AcOH after the evaporation. The residue was extracted by H_2O and ethyl acetate (20 mL \times 2). The organic layers were washed with brine and dried with $MgSO_4$. Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 4:1) afforded starting material **1** (0.26 g) and compound **24** (0.16 g, 36% yield, 96% conversion). 1H NMR (300 MHz, $CDCl_3$) δ 1.71 (s, 6H), 4.52 (dt, J = 4.2, 0.9 Hz, 2H), 5.30 (m, 1H), 5.39 (m, 1H), 5.98 (m, 1H), 6.00 (d, J = 1.5 Hz, 1H), 6.13 (d, J = 1.5 Hz, 1H), 10.41 (s, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8, 69.4, 93.3, 95.4, 96.6, 107.1, 118.7, 132.2, 157.1, 163.2, 165.4, 166.8. TLC (ethyl acetate: hexane = 1:2) R_f = 0.62.

7-Allyloxy-5-benzensulfonyloxy-2,2-dimethylbenzo[1,3]dioxin-4-one (25)

To compound **24** (0.24 g, 0.96 mmol) in 20 mL of THF at 0 °C was added Et_3N (0.3 g, 3 mmol), followed by slow addition of benzenesulfonyl chloride (0.44 g, 2.5 mmol). The mixture was warmed slowly to room temperature and stirred overnight. The solution was neutralized by 0.5M aqueous AcOH and extracted with H_2O and ethyl acetate (20 mL \times 2). The organic layers were washed with brine and dried with $MgSO_4$. Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 2:1) afforded compound **25** (0.36 g, 96% yield) as a white solid: m. p. 99 -101 °C; 1H NMR (300 MHz, $CDCl_3$) δ 1.60 (s, 6H), 4.55 (dt, J = 5.4, 1.2 Hz, 2H), 5.33-5.46 (m, 2H), 5.99 (m, 1H), 6.38 (d, J = 2.4 Hz, 1H), 6.67 (d, J = 2.4 Hz, 1H), 7.55 (m, 2H), 7.68 (m, 1H), 8.03 (m, 1H), 8.06

(m, 1H); MS m/z 390, 331, 190, 141, 76; HRMS m/z for $C_{19}H_{18}O_7S$ calcd. 390.0773, measured 390.0779. TLC (ethyl acetate: hexane = 1:2) R_f = 0.39.

1-(4-Allyloxy-2-benzenesulfonyloxy-6-hydroxyphenyl)-2-methylbutan-1-one (26)

To compound **25** (0.15 g, 0.38 mmol) in 20 mL of THF at $-78\text{ }^{\circ}\text{C}$ was added *sec*-BuLi (1.4 M, 0.6 mL, 0.83 mmol) slowly. After 10 minutes at $-78\text{ }^{\circ}\text{C}$, 0.1 mL of glacial AcOH was added. The mixture was warmed slowly to $0\text{ }^{\circ}\text{C}$ and extracted with H_2O and ethyl acetate (20 mL \times 2). The organic layers were washed with brine and dried with $MgSO_4$. Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 6:1) afforded compound **25** (61 mg, 41% yield). 1H NMR (300 MHz, $CDCl_3$) δ 0.80 (t, J = 7.5 Hz, 3H), 1.04 (d, J = 6.9 Hz, 3H), 1.33 (m, 1H), 1.66 (m, 1H), 3.43 (m, 1H), 4.46 (dt, J = 5.4, 1.5 Hz, 2H), 5.28-5.39 (m, 2H), 5.94 (m, 1H), 6.20 (d, J = 2.7 Hz, 1H), 6.33 (d, J = 2.7 Hz, 1H), 7.56 (m, 2H), 7.70 (m, 1H), 7.84 (m, 2H), 12.85 (s, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.7, 16.3, 27.1, 46.0, 69.4, 101.3, 102.7, 108.7, 118.9, 128.7, 129.6, 132.0, 135.0, 135.3, 150.6, 163.3, 165.9, 209.4. TLC (ethyl acetate: hexane = 1:2) R_f = 0.73.

1-(2,4-Bis-allyloxy-6-benzenesulfonyloxyphenyl)-2-methylbutan-1-one (27)

To compound **26** (30 mg, 0.077 mmol) and anhydrous K_2CO_3 (32 mg, 0.23 mmol) in 5 mL of acetone at $0\text{ }^{\circ}\text{C}$ was added allyl bromide (24 mg, 0.2 mmol). The mixture was warmed slowly to room temperature and stirred overnight. The solution was neutralized by 0.5M aqueous AcOH, extracted with H_2O and ethyl acetate (10 mL \times 2). The organic layers were washed with brine and dried with $MgSO_4$. Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 2:1) afforded compound **27** (32 mg, 97%

yield). ^1H NMR (300 MHz, CDCl_3) δ 0.84 (t, $J = 7.5$ Hz, 3H), 1.01 (d, $J = 7.2$ Hz, 3H), 1.29 (m, 1H), 1.67 (m, 1H), 2.80 (m, 1H), 4.44-4.49 (m, 4H), 5.21-5.43 (m, 4H), 5.87-5.97 (m, 2H), 6.35 (d, $J = 2.1$ Hz, 1H), 6.55 (d, $J = 2.1$ Hz, 1H), 7.54 (m, 2H), 7.67 (m, 1H), 7.89 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 11.7, 14.9, 25.2, 49.0, 69.5, 69.7, 99.3, 99.9, 118.2, 118.3, 118.7, 128.8, 129.4, 132.3, 132.5, 134.7, 135.7, 147.6, 157.3, 160.4, 204.9; MS m/z 430, 373, 141, 76; HRMS m/z for $\text{C}_{23}\text{H}_{26}\text{O}_6\text{S}$ calcd. 430.1450, measured 430.1456. TLC (ethyl acetate: hexane = 1:2) R_f = 0.19.

5-Hydroxy-7-methoxymethoxy-2-phenylchromen-4-one (30)³²

To chrysin 6 (0.38 g, 1.5 mmol) in 10 mL of DMF at 0 °C was added *i*-Pr₂NEt (0.39 g, 3 mmol), followed by MOMCl (0.24 g, 3 mmol). After 10 minutes, the temperature was increased to room temperature and stirred overnight. Twenty mL of H₂O was added to precipitate the product. The precipitate was collected by filtration, and dissolved in 20 mL of CH_2Cl_2 . The organic layers were washed with brine and dried with MgSO_4 . Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 2:1) afforded compound 30 (0.42 g, 95% yield). NMR (300 MHz, CDCl_3) δ 3.51 (s, 3H), 5.25 (s, 2H), 6.49 (d, $J = 2.1$ Hz, 1H), 6.68 (s, 1H), 6.69 (d, $J = 2.1$ Hz, 1H), 7.52 (m, 3H), 7.89 (m, 2H).

5-Hydroxy-3-(hydroxybenzyl)-7-methoxymethoxy-2-phenylchromen-4-one (31)

To 2,2,6,6-tetramethylpiperidine (71 mg, 0.5 mmol) in 5 mL of THF at 0 °C was added *n*-BuLi (2.1M, 0.24 mL, 0.5 mmol) dropwise. After 1 h at 0 °C, compound 30 (60 mg, 0.2 mmol) in 2 mL of THF was added slowly. After one more hour at 0 °C, the temperature was cooled to -78 °C, and benzaldehyde (53 mg, 0.5 mmol) in 2 mL of THF was added

slowly. When the mixture was warmed slowly to $-30\text{ }^{\circ}\text{C}$ in 30 min, the reaction was shown to be complete by TLC plate monitoring. The solution was neutralized by 0.5M aqueous AcOH and extracted by H_2O and ethyl acetate ($10\text{ mL} \times 2$). The organic layers were washed with brine and dried with MgSO_4 . Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 4:1) afforded compound **31** (51 mg, 63% yield). ^1H NMR (300 MHz, CDCl_3) δ 3.49 (s, 3H), 4.85 (d, $J = 11.4\text{ Hz}$, OH), 5.23 (s, 2H), 5.70 (d, $J = 11.4\text{ Hz}$, 1H), 6.48 (d, $J = 2.1\text{ Hz}$, 1H), 6.64 (d, $J = 2.1\text{ Hz}$, 1H), 7.27-7.61 (m, 10H); ^{13}C NMR (75 MHz, CDCl_3) δ 56.7, 72.0, 94.47, 94.52, 100.5, 106.4, 119.7, 126.0, 127.7, 128.7, 128.8, 129.0, 129.1, 131.4, 131.8, 143.1, 157.9, 162.3, 163.7, 163.8; MS m/z 404, 403, 385, 353, 326, 298, 280, 191, 104; HRMS m/z for $\text{C}_{24}\text{H}_{20}\text{O}_6\text{S}$ calcd. 404.1260, measured 404.1266. TLC (ethyl acetate: hexane = 1:2) $R_f = 0.51$.

5,7-Bisbenzyloxy-2-phenylchromen-4-one (**32**)

To chrysin **6** (0.5 g, 2 mmol) and anhydrous K_2CO_3 (1.66 g, 12 mmol) in 60 mL of acetone at room temperature was added BnBr (1.71 g, 10 mmol). The mixture was heated to $72\text{ }^{\circ}\text{C}$ for 24 hours. The solution was cooled to room temperature and vacuum evaporation removed most of the solvent. The residue was extracted by H_2O and ethyl acetate ($30\text{ mL} \times 2$). The organic layers were washed with brine and dried with MgSO_4 . Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 4:1) afforded compound **18** (0.83 g, 97% yield). ^1H NMR (300 MHz, CDCl_3) δ 5.12 (s, 2H), 5.24 (s, 2H), 6.51 (d, $J = 2.1\text{ Hz}$, 1H), 6.66 (d, $J = 2.1\text{ Hz}$, 1H), 6.68 (s, 1H), 7.21-7.46 (m, 10H), 7.51 (m, 3H), 7.62 (m, 2H), 7.88 (m, 2H); MS m/z 434, 91; HRMS m/z for $\text{C}_{29}\text{H}_{22}\text{O}_4$ calcd. 434.1518, measured 434.1526. TLC (ethyl acetate: hexane = 1:2) $R_f = 0.19$.

5,7-Bisbenzyloxy-8-iodo-2-phenylchromen-4-one (33)

To compound **32** (0.37 g, 0.85 mmol) in 10 mL of anhydrous DMSO and 10 mL of glacial AcOH co-solvent at 0 °C was slowly added ICl solution (1 M, 1.7 mL, 1.7 mmol). The solution was warmed slowly to room temperature and stirred in the dark for 24 hours. Ten mL of saturated Na₂S₂O₃ was added to reduce the remaining iodine. The solution was extracted with ethyl acetate (30 mL × 2) and saturated NaHCO₃, brine, and dried with MgSO₄. Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 4:1) afforded compounds **33** and **32** (0.40 g, 86% yield) in 6:1 ratio based on ¹H NMR spectrum. ¹H NMR (300 MHz, CDCl₃) δ 5.19 (s, 2H), 5.24 (s, 2H), 6.48 (s, 1H), 6.73 (s, 1H), 7.30-7.57 (m, 13H), 8.07 (m, 2H).

5,7-Bisbenzyloxy-8-(3-dimethylaminoprop-1-ynyl)-2-phenylchromen-4-one (34)

Compound **32** (0.01 mmol) and compound **33** (0.03 mmol) (23 mg) were dissolved in 5 mL of Et₃N and 1 mL of acetonitrile, followed the addition of *N,N*-dimethylpropagylamine (25 mg, 0.3 mmol), Pd(PPh₃)₄ (1.7 mg, 0.03 mmol × 5%), and CuI (0.5 mg, 0.03 mmol × 20%). The mixture was heated to 60 °C for 24 hours under an argon atmosphere. After the mixture was cooled to room temperature, vacuum evaporation removed most of the solvent. The residue was extracted by H₂O and ethyl acetate (10 mL × 2). The organic layers were washed with brine and dried with MgSO₄. Evaporation of the solvent and purification by flash chromatography (ethyl acetate) afforded compound **34** (14 mg, 90% yield) as a light yellow solid. ¹H NMR (300 MHz, CDCl₃) δ 2.38 (s, 6H), 3.68 (s, 2H), 5.18 (s, 2H), 5.24 (s, 2H), 6.45 (s, 1H), 6.69 (s, 1H), 7.30-7.44 (m, 8H), 7.45-7.57 (m, 5H), 7.98 (m, 2H).

5,7-Bisbenzyloxy-2-phenyl-8-pyridin-4-ylchromen-4-one (35)

To compound **32** (0.016 mmol) and compound **33** (0.05 mmol) (36 mg) and 4-pyridylboronic acid pinacol ester (16 mg, 0.08 mmol) in a sealed tube was added Na_2CO_3 (53 mg, 0.5 mmol), $\text{Pd}(\text{PPh}_3)_4$ (3 mg, 0.05 mmol \times 5%), which were followed with 1 mL of H_2O , 2 mL of EtOH, and 3 mL of 1,4-dioxane. Under an argon atmosphere, the mixture was heated at 100 °C for 24 hours. After the mixture was cooled to room temperature, it was extracted by H_2O and ethyl acetate (15 mL \times 3). The organic layers were washed with brine and dried with MgSO_4 . Evaporation of solvent and purification by flash chromatography (ethyl acetate: hexane = 1:1) afforded compound **35** (23 mg, 92% yield). ^1H NMR (300 MHz, CDCl_3) δ 5.09 (s, 2H), 5.29 (s, 2H), 6.58 (s, 1H), 6.69 (s, 1H), 7.18 (m, 2H), 7.31-7.58 (m, 15H), 8.72 (d, J = 6 Hz, 2H). MS: m/z 511, 420, 404, 389, 91. HRMS: m/z for $\text{C}_{34}\text{H}_{25}\text{NO}_4$ calcd. 511.1784, measured 511.1793. TLC (ethyl acetate: hexane = 1:1) R_f = 0.18.

5,7-Dihydroxy-2-phenyl-8-pyridin-4-ylchromen-4-one (36)

To compound **35** (51 mg, 0.1 mmol) in 10 mL of CH_3OH and 10 mL of CH_2Cl_2 was added trifluoroacetic acid (1 M in CH_2Cl_2 , 0.2 mL). The solution was evacuated by water aspirator until the solvent was bubbling and flushed with H_2 gas. This operation was repeated three times before the Pd/C (10 mg) addition. After the Pd/C addition, this evacuation / H_2 gas flush was repeated three times. The mixture was stirred under H_2 gas at room temperature overnight. When the reaction was complete, Et_3N (1 M in CH_2Cl_2 , 0.2 mL) was added and the mixture was filtered through Celite. The filtrate was concentrated. The residue was washed by CH_2Cl_2 (5 mL \times 3) to afford compound **36** (33 mg, 100%). ^1H NMR (300 MHz, CD_3OD) δ 6.44 (s, 1H), 7.04 (s, 1H), 7.41-7.57 (m, 5H), 7.75 (d, J = 6.9 Hz, 2H),

8.67 (d, $J = 4.5\text{Hz}$, 2H), 11.22 (s, OH), 13.10 (s, OH); MS m/z 331, 277, 85; HRMS m/z for $\text{C}_{20}\text{H}_{13}\text{NO}_4$ calcd. 331.0845, measured 331.0848. TLC (ethyl acetate) $R_f = 0.62$.

References:

1. Lee, K. H. *J. Biomed. Sci.* **1996**, *6*, 236-250.
2. Chandle, F. R.; Freeman, L.; Hooper, S. N. *J. Ethnopharmacol* **1979**, *1*, 49-68.
3. Hollman, P. C. H.; Katan, M. B. *Food and Chemical Toxicology* **1999**, *37*, 937-942.
4. Middleton, E. and Kandaswami, C. In *The Flavonoids: Advances in Research Since 1986*, ed. Harborne, J. B. 1st edn, **1994**, 619-652. Chapman & Hall, London.
5. Spencer, J. P. E.; Rice-Evans, C. A.; Schroeter, H. In *Flavonoids in Health and Disease*, Rice-Evans, C. A.; Packer, L. ED.; Marcel Dekker, New York, 2nd edn., **2003**, 309-347.
6. Bohm, B. A.; Stuessy, T. F. In *Flavonoids of the Sunflower Family (Asteraceae)*; Springer-Verlag/Wien, New York **2001**, 123-134.
7. Boumendjel, A. *Curr. Med. Chem.* **2003**, *10*, 2621-2630.
8. Kosasi, S.; van der Sluis, W. G.; Labadie, R. P. *Phytochemistry* **1989**, *28*, 2439-2441.
9. Bohr, G.; Gerhauser, C.; Knauff, J.; Zapp, J.; Becker, H. *J. Nat. Prod.* **2005**, *68*, 1545-1548.
10. Gibbons, S.; Moser, E.; Hausmann, S.; Stavri, M.; Smith, E.; Clennett, C. *Phytochemistry* **2005**, *66*, 1472-1475.
11. Pecchio, M.; Solis, P. N.; Lopez-Perez, J. L.; Vasquez, Y.; Rodriguez, N.; Olmedo, D.; Correa, M.; Feliciano, A. S.; Gupta, M. P. *J. Nat. Prod.* **2006**, *69*, 410-413.
12. Iikubo, K.; Ishikawa, Y.; Ando, N.; Umezawab, K.; Nishiyamaa, S. *Tetrahedron Lett.* **2002**, *43*, 291-293.

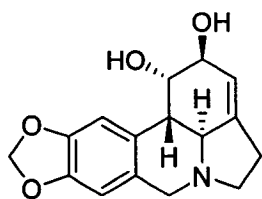
13. Wagner, H.; Farkas, L. In *The Flavonoids, Part 1*, ed. Harborne, J. B.; Mabry, T. J.; Mabry, H. **1975**, 127-213. Academic Press, New York.
14. Wheeler, T. S. *Org. Syn.* **1952**, *32*, 72-76.
15. (a) Mahal, H. S.; Rai, H. S.; Venkataraman, K. *J. Chem. Soc.* **1935**, 866-868. (b) Reichel, L.; Steudel, J. *Ann.* **1942**, *553*, 83-97.
16. Garcia, H.; Iborra, S.; Primo, J.; Miranda, M. A. *J. Org. Chem.* **1986**, *51*, 4432-4436.
17. (a) Kalinin, V. N.; Shostakovskii, M. V.; Ponomarev, A. B. *Doklady Akademii Nauk SSSR.* **1990**, *312*, 1142-1144 (b) Ciattini, P. G.; Morera, E.; Ortar, G.; Rossi, S. S. *Tetrahedron*, **1991**, *47*, 6449-6456.
18. Nakayama, T.; Sato, T.; Fukui, Y.; Yonekura-Sakakibara, K.; Hayashi, H.; Tanaka, Y.; Kusumi, T.; Nishino, T. *FEBS Lett.* **2001**, *499*, 107-111.
19. Kayser, Oliver; Kiderlen, Albrecht F.; Brun, Reto. *Planta Medica*, **2001**, *67*, 718-721.
20. Kayser, Oliver; Kiderlen, Albrecht F. *Tokai J. Exp. Clin. Med.* **1998**, *23*, 423-426.
21. Varma, R. S.; Varma, M. *Tetrahedron Lett.* **1992**, *33*, 5937.
22. (a) Beney, C.; Mariotte, A. M.; Boumendjel, A. *Heterocycles*, **2001**, *55*, 967-972. (b) Adams, C. J.; Main, L. *Tetrahedron* **1992**, *48*, 9929. (c) Gurjar, M. K. *Current Science* **1978**, *47*, 887-888.
23. (a) Howells, H. P.; Little, J. G. *J. Am. Chem. Soc.* **1932**, *54*, 2451-2453. (b) Shriner, R. L.; Grosser, F. *J. Am. Chem. Soc.* **1942**, *64*, 382-384.
24. (a) Kolokythas, G.; Kostakis, I. K.; Pouli, N.; Marakos, P.; Kletsas, D.; Pratsinis, H. *Bio. Med. Chem.* **2003**, *11*, 4591-4598. (b) Friscic, T.; Drab, D. M.; MacGillivray, L. R. *Org. Lett.* **2004**, *6*, 4647-4650.

25. Gokan, N.; Kikuchi, H.; Nakamura, K.; Oshima, Y.; Hosaka, K.; Kubohara, Y.
Biochem. Pharm. **2005**, *70*, 676-685.
26. Chen, Zh.; Hu, Y.; Wu, H.; Jiang, H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3949-3952.
27. Dushin, R. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1992**, *114*, 655-659.
28. Kamisuki, S.; Takahashi, S.; Mizushima, Y.; Hanashima, S.; Kuramochi, K.; Kobayashi, S.; Sakaguchi, K.; Nakatab, T.; Sugawara, F. *Tetrahedron* **2004**, *60*, 5695-5700.
29. Viola, H.; Wasowski, C.; Levi de Stein, M.; Wolfman, C.; Silveira, R.; Dajas, F.; Medina, J. H.; Paladini, A. C. *Planta Medica* **1995**, *61*, 213-16.
30. de Azevedo, W. F., Jr.; Mueller-Dieckmann, H.; Schulze-Gahmen, U.; Wordland, P. J.; Sausville, E.; Kim, S. *Proc. Natl. Acad. Sci.* **1996**, *93*, 2735-2740.
31. Getman, C. R.; Bible, K. C. *Recent Res. Develp. Cancer*, **2004**, *6*, 37-56.
32. Daskiewicz, J.; Bayet, C.; Barron, D. *Tetrahedron* **2002**, *58*, 3589-3595.

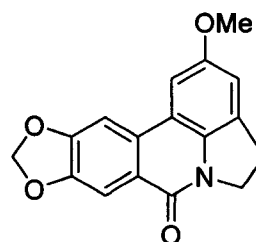
CHAPTER 5. SYNTHESIS OF LYCORINES

Introduction:

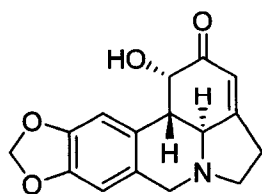
Severe Acute Respirator Syndrome (SARS) is a respiratory illness caused by Severe Acute Respirator Syndrome corona virus (SARS-CoV), which was first identified in 2003.¹⁻³ It is highly contagious and life threatening. There is currently no universal treatment system that has been developed for SARS-CoV. It is therefore very important to have a drug to combat the virus in the event of an outbreak in the future. A study was done on Chinese medicinal herb extracts to identify natural compounds with antiviral activities against SARS-CoV.⁴ More than 200 Chinese medicinal herb extracts were screened. After further purification and activity studies, lycorine (1) was shown to be a strong candidate as a potential antiviral drug against SARS-CoV.⁴



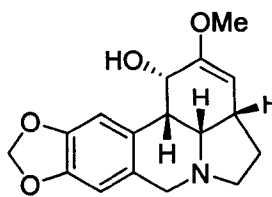
Lycorine (1)



Oxogalanthine lactam (2)



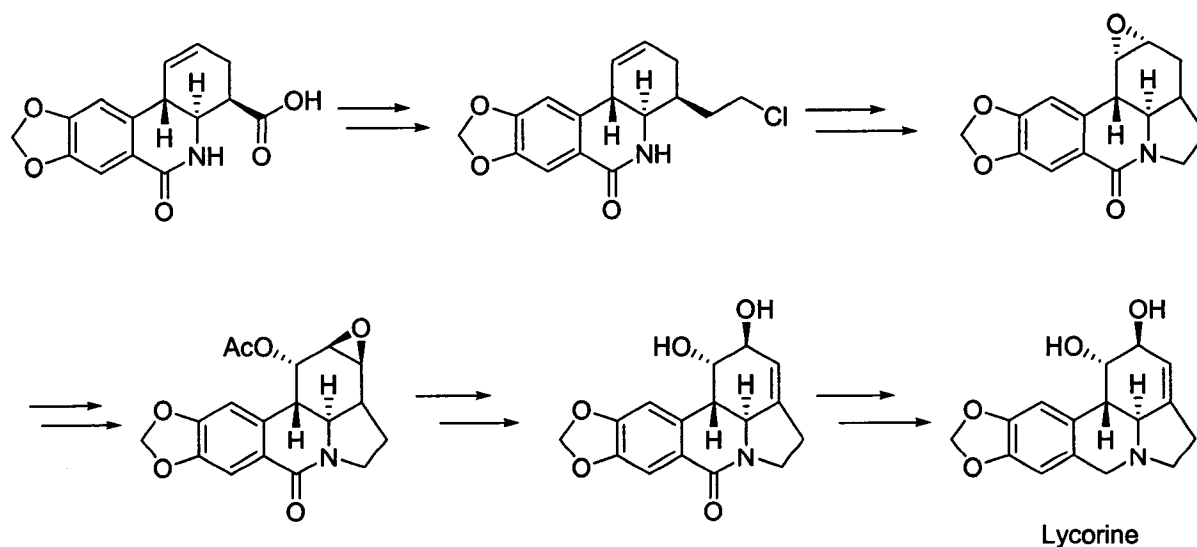
2-Oxolycorine (3)



Amarbellisine (4)

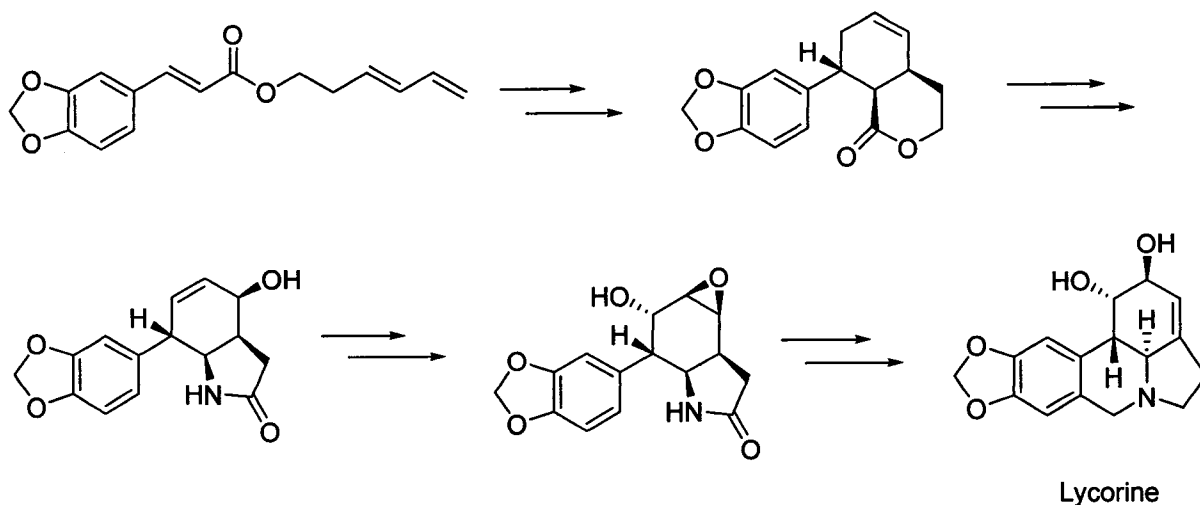
Lycorine (1), the major alkaloid constituent of the *Amaryllidaceae* family and the first alkaloid isolated from *Amaryllidaceae* family in 1920,⁵ has other biological activities, which include antineoplastic and anti-inflammatory activity, inhibitory effect on tumor cell apoptosis, and DNA binding activity.⁵ Lycorine-type alkaloids also include oxogalanthine lactam (2),⁶ 2-oxolycorine (3),⁵ and amarbellisine (4).⁷

Lycorine has been an attractive synthetic target for exploring new synthetic methodology, since its structure bears four continuous stereogenic centers arranged in all-*anti* relationships. Although there have been many synthetic studies on lycorine,⁸⁻¹⁴ the first total synthesis of lycorine was reported by Tsuda in 1979.¹⁵ The synthesis of lycorine was accomplished starting from a tetracyclic carboxylic acid compound. The pentacyclic skeleton was constructed by intramolecular alkylation. After two epoxidation and epoxide opening reactions to introduce double bonds, lycorine was achieved by lactam reduction.

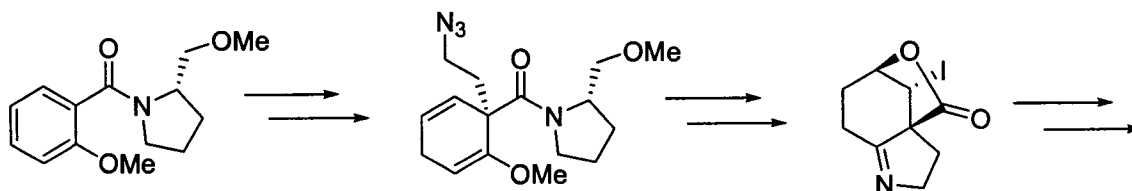


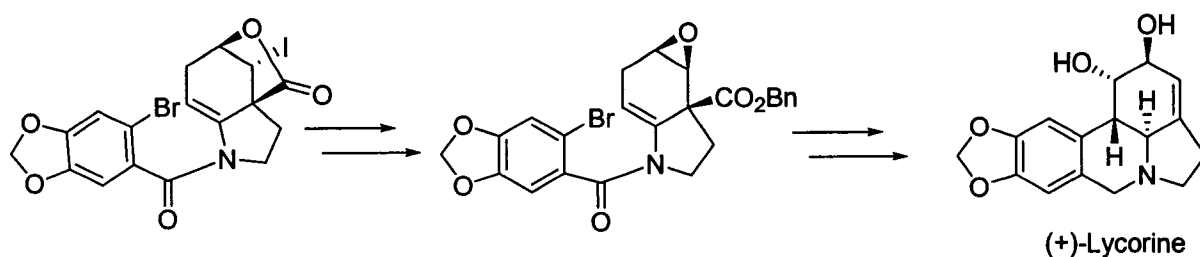
In 1996, Hoshino reported the total synthesis of lycorine starting from a triene ester.¹⁶

The key step involved an intramolecular Diels-Alder reaction to control two of the four stereogenic centers of lycorine. Introduction of functional groups on the six-membered ring by epoxidation and Payne rearrangement afforded an epoxy alcohol, which was converted into lycorine by acyl iminium ion cyclization and other functionalizations.

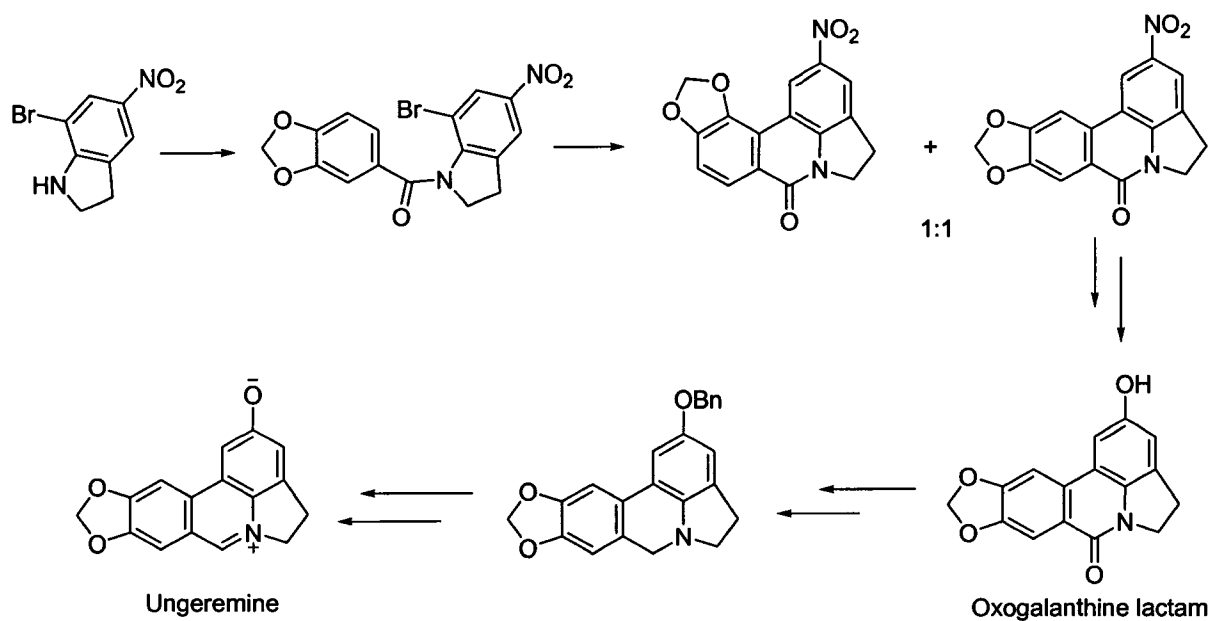


In the first total synthesis of optically active (+) lycorine,¹⁷ Birch reduction-alkylation and transformation of functionalized indoline derivatives constituted key reactions. Radical-mediated cyclization produced the key pentacyclic intermediate, which underwent further functionalization to achieve (+) lycorine.





Oxogalanthine lactam (**2**) was found to bind to A1 adenosine receptors with K_i value of 5-6 μM .^{6(b)} This finding may set the stage for the development of novel adenosine antagonists. Oxogalanthine lactam has been reported as an intermediate in the total synthesis of ungeremine,¹⁸ which was isolated from *Ungernia minor* in 1965.¹⁹ Radical cyclization was the key reaction to construct the pentacyclic skeleton. However, under the radical conditions, the bromonitro precursor gave two regioisomers in 1:1 ratio. The expected product was obtained in 27% yield.

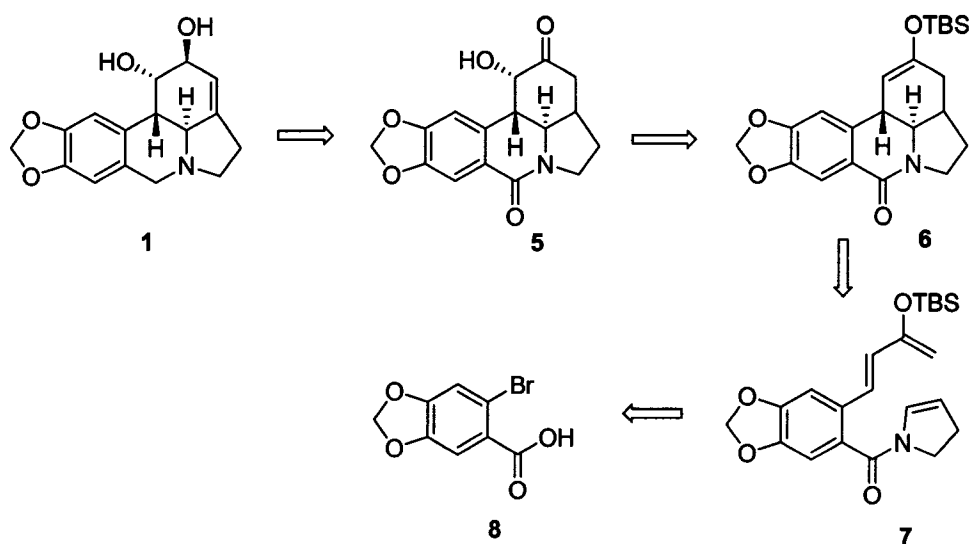


Although there are many synthetic studies and significant achievements on the synthesis of lycorines, all the reported syntheses constructed the tricyclic core skeleton by making one ring at a time. More efficient ring cyclizations for this important drug candidate need to be developed.

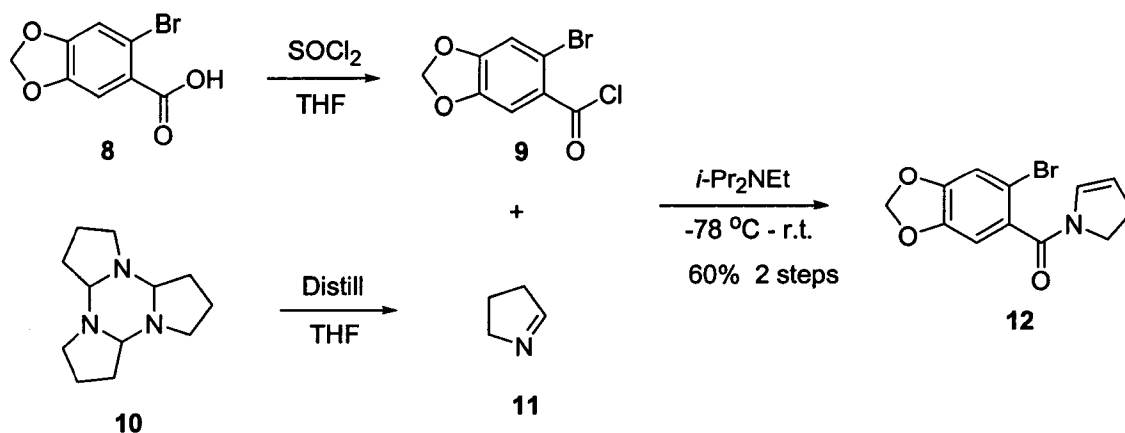
Results and Discussion:

As shown in the retrosynthetic analysis, lycorine (**1**) could be achieved from α -hydroxy ketone **5** by introducing an α , β -unsaturated enone double bond and selective carbonyl reductions. Compound **5** is derived from enol ether **6** by an epoxidation reaction. Compound **6** is the key intermediate in our synthesis. The pentacyclic skeleton is constructed by an intramolecular Diels-Alder reaction. The Diels-Alder precursor **7** is derived from the commercially available starting material 6-bromo-3,4-methylenedioxybenzoic acid **8**.

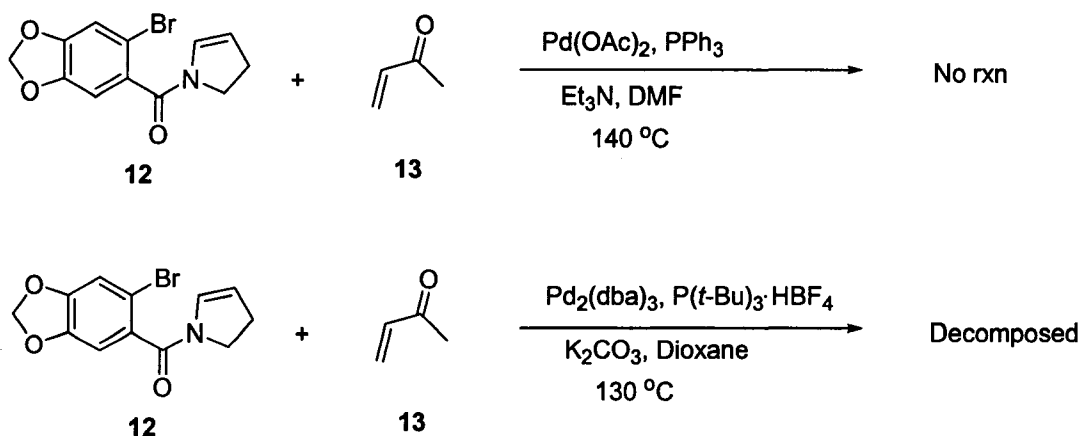
This design not only provides a more direct synthesis of lycorine, but also has the advantage that other lycorine-type alkaloids can be synthesized. Oxidation of intermediate **6** will lead to oxogalanthine lactam (**2**). The chemistry developed in our group to synthesize *N*-acyl-2-pyrrolines²⁰ will be applied to prepare the dienophile moiety of Diels-Alder precursor **7**.



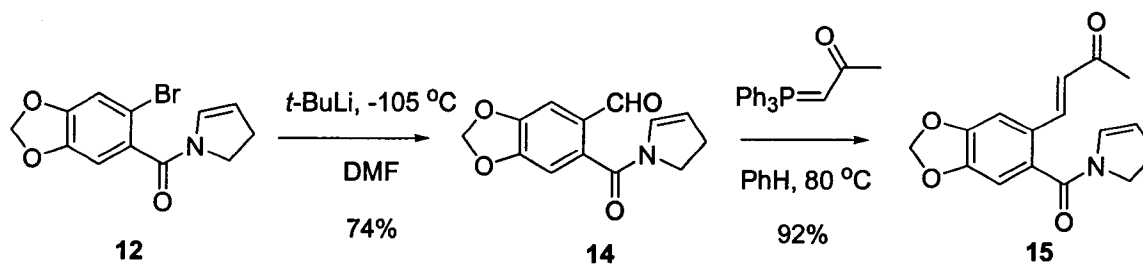
Commercially available starting material 6-bromo-3,4-(methylenedioxy)benzoic acid (8) can also be prepared by aldehyde oxidation²¹ in excellent yield. To apply the facile synthesis of *N*-acyl-2-pyrrolines, compound 8 was converted to acid chloride 9 by thionyl chloride in THF at 50 °C. The 1-pyrroline monomer 11 was distilled as an azeotrope with THF from the 2,3,4,5-tetrahydropyridine trimer.²² In the presence of diisopropyl ethyl amine, acid chloride 9 was transferred to freshly distilled 1-pyrroline monomer 11 at -78 °C. The mixture was warmed slowly to room temperature to provide *N*-acyl-2-pyrroline compound 12 in 60% yield over two steps.



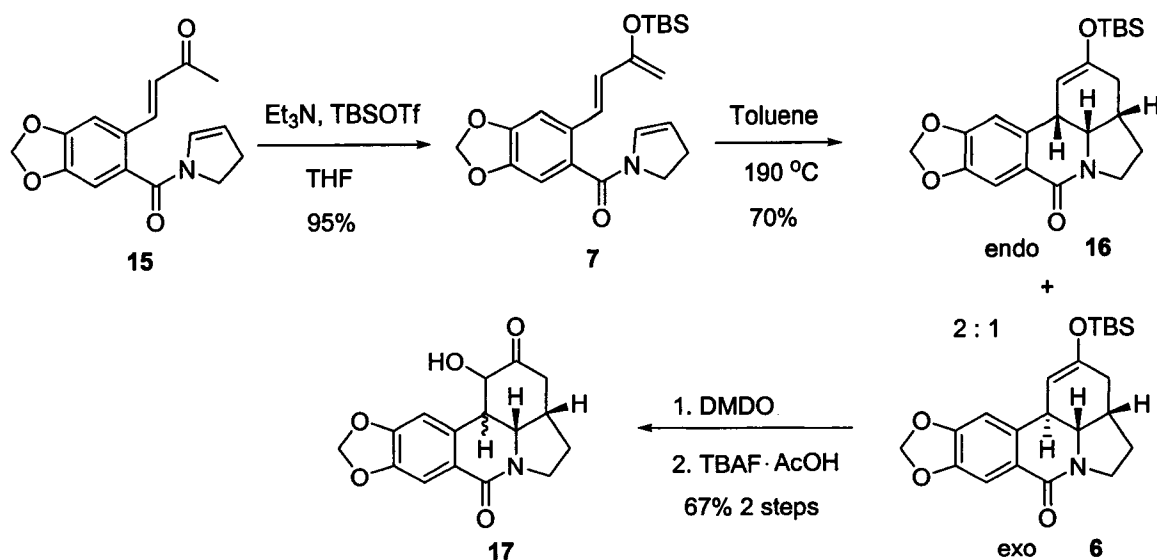
The Heck reaction of **12** with methyl vinyl ketone **13** should be the most straightforward conversion to **15**. Unfortunately, no reaction occurred when $\text{Pd}(\text{OAc})_2$ was chosen as catalyst in DMF solution. When using $\text{Pd}_2(\text{dba})_3$, $\text{P}(t\text{-Bu})_3$, and K_2CO_3 in dioxane at 130 °C, the starting material **12** decomposed.



Because of the unsuccessful Heck reactions, bromo compound **12** was first converted into aldehyde **14** by metal halogen exchange using *tert*-BuLi and DMF. Compound **14** was unstable in solution at room temperature, but is stable neat at -20 °C. Wittig reaction of **14** afforded *trans*-enone **15** in excellent yield.

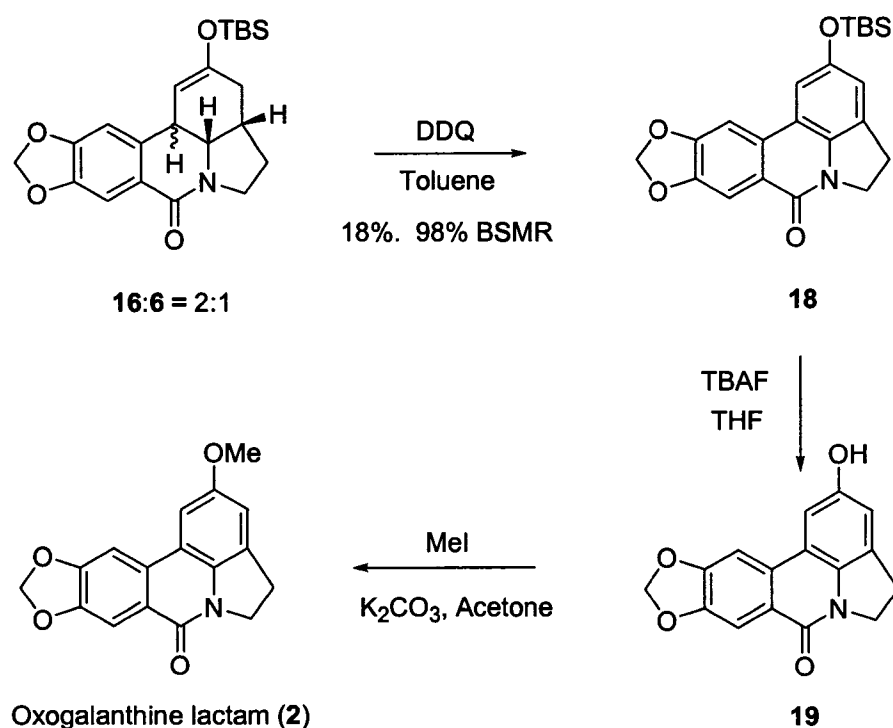


Enone **15** was treated with triethylamine and TBSOTf in THF to give Diels-Alder precursor **7** in excellent yield. The Diels-Alder reaction was sensitive to reaction temperature and to starting material concentration. A dilute solution gave higher yields. At 180 °C in toluene, the reaction was not complete after six hours. If the temperature was higher than 200 °C, a three component mixture was obtained instead of Diels-Alder adducts. Using toluene as the solvent at 190 °C gave the Diels-Alder adducts in 70% yield with *endo*:*exo* adducts in 2:1 ratio. The *endo* product **16** and *exo* product **6** were inseparable by flash silica gel chromatography. After the unsuccessful *m*CPBA epoxidation, dimethyl dioxirane (DMDO) was a good oxidizing agent. Oxidation with DMDO followed by TBS deprotection afforded α -hydroxy ketone **17**.

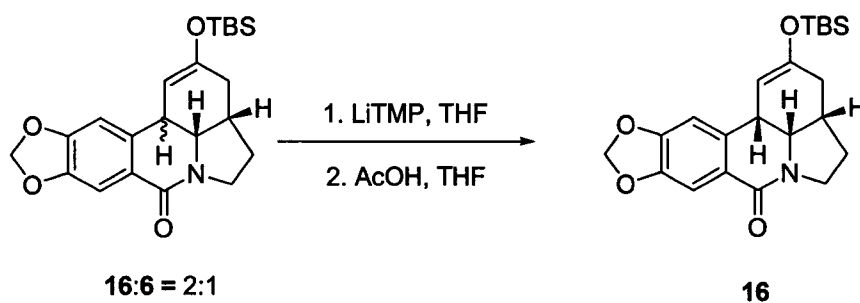


The oxidation of Diels-Alder adducts using DDQ in toluene afforded lactam **18**. TBS deprotection, followed by methylation, would lead to oxogalanthine lactam (**2**). However, the TBS deprotection of compound **18** using TBAF in THF did not provide clean **19**,

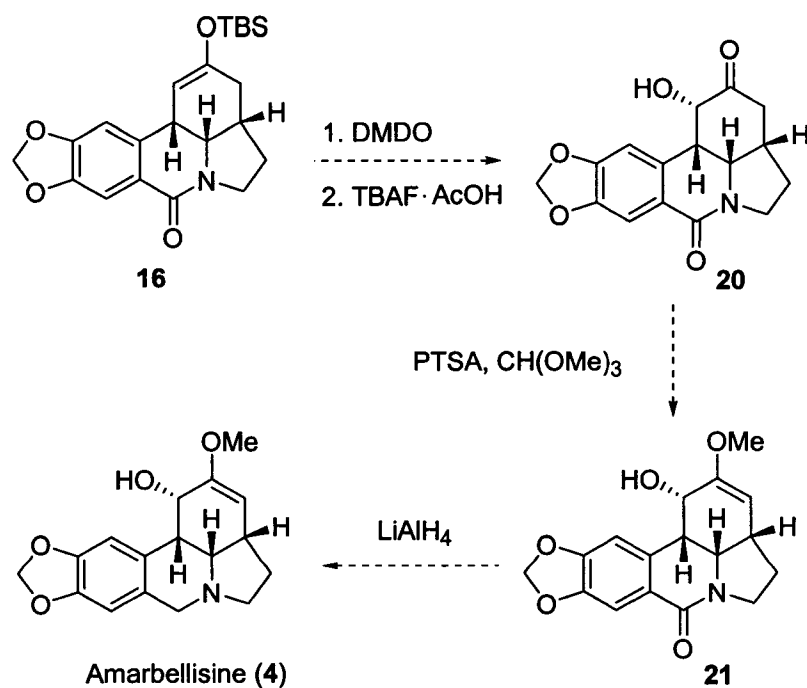
although the main peaks on compound **19**'s ^1H NMR spectrum were able to be identified. Crude **19** was methylated using MeI and K_2CO_3 in acetone to give a methylated crude product **2**. Unfortunately, the characters of its ^1H NMR spectrum were different from the reported compound.²³ So, structures of the final product and intermediates would be checked in the future.



The direct epimerization of Diels-Alder adducts **16** and **6** was investigated. When the 2:1 mixture was treated with LiTMP in THF and quenched with AcOH, the kinetic *cis* product **16** was the main product (16:6 = 20:1) based on ^1H NMR spectrum. Since this reaction was only done once in small scale, further optimizations would be done in the future.



Although the *cis* stereochemistry is not good for lycorine synthesis, compound **16** will be a key intermediate for another lycorine-type alkaloid, amarbellicine (**4**). An epoxidation using DMDO (Dimethyl Dioxirane) would be expected to give ketone **20**, which would be treated with PTSA and methyl formate to form methyl enol ether **21**. A carbonyl reduction would achieve amarbellicine (**4**).



In summary, the pentacyclic lycorine skeleton has been constructed by an intramolecular Diels-Alder reaction. A facile *N*-acyl-2-pyrroline synthesis has been used to prepare the dienophile. The lycorine intermediate would be applied to the total synthesis of oxogalanthine lactam (**2**), amarbellithine (**4**), and other lycorine type alkaloids.

Experimental Section

Unless stated otherwise, reactions were performed in flame-dried glassware under an argon atmosphere, using freshly distilled solvents. Diethyl ether (Et₂O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methylene chloride (CH₂Cl₂), benzene, toluene and diisopropylamine (*i*-Pr₂NH) were distilled from calcium hydride. *N,N*-Dimethyl formamide (DMF), dimethyl sulfoxide (DMSO), and hexamethylphosphoramide (HMPA) were distilled from calcium hydride and stored over activated 4 Å molecular sieves in sealed containers.

Unless stated otherwise, all reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) plates purchased from Aldrich (Cat. No. Z122785-25EA). Column or flash chromatography (silica) was performed with the indicated solvents using standard grade silica gel (particle size 230-400 mesh, 60 Å).

¹H and ¹³C NMR spectra were obtained on either a Varian 300 MHz or a Bruker 400 MHz spectrometer. Chemical shifts are reported relative to internal Me₄Si (¹H and ¹³C, δ 0.00 ppm) or chloroform (¹H, δ 7.26 ppm; ¹³C, δ 77.0 ppm). All melting points were obtained on a MEL-TEMP II variable temperature melting point apparatus from Laboratory Devices and are uncorrected. High-resolution mass spectra were recorded on a Kratos model

MS-50 spectrometer, and low-resolution mass spectra were recorded on a Finnegan 4023 mass spectrometer.

6-Bromobenzo[1,3]dioxole-5-carbonylchloride (9)

To 6-bromo-3,4-methylenedioxybenzoic acid **8** (1.17 g, 4.8 mmol) in 20 mL of THF at 0 °C was added thionyl chloride (0.58 g, 5.3 mmol) slowly. The mixture was stirred and warmed slowly to room temperature, then heated to 50 °C overnight. After the solution was cooled to room temperature, the solvent was removed in vacuo. The solid product was used directly for the next step. ¹H NMR (300 MHz, CD₃COCD₃) δ 6.25 (s, 2H), 7.29 (s, 1H), 7.64 (s, 1H).

(6-Bromobenzo[1,3]dioxol-5-yl)-(2,3-dihydropyrrol-1-yl)methanone (12)

Crude 2,3,4,5-tetrahydropyridine trimer (0.5 g, 2.4 mmol) was distilled with 25 mL of THF to give 1-pyrroline monomer **11** azeotrope with THF which was collected at -78 °C. To the above distillate at -78 °C was added *i*-Pr₂NEt (1.3 g, 10 mmol), followed by the freshly made **9** in 15 mL of THF. The mixture was stirred and warmed slowly to room temperature. After one more hour at room temperature, the solution was extracted with H₂O and ethyl acetate (30 mL × 2), washed with brine, and dried with MgSO₄. Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 2:1) afforded product **12** (1.42 g, 60% yield over two steps) as a light yellow solid. ¹H NMR (300 MHz, CDCl₃) δ 2.69-2.76 (m, 2H), 3.60 & 4.00 (t, *J* = 8.7 Hz, 2H), 5.20-5.23 & 5.36-5.40 (m, 1H), 6.01 (s, 2H), 6.03-6.06 & 7.03-7.05 (m, 1H), 6.76 & 6.78 (s, 1H), 6.99 & 7.00 (s, 1H); MS

m/z 295 & 296, 227 & 228, 199 & 200, 143; HRMS m/z for $C_{12}H_{10}O_3NBr$ calcd. 295.9922, meads. 295.9926. TLC (ethyl acetate: hexane = 1:1) R_f = 0.37.

6-(2,3-Dihydropyrrole-1-carbonyl)benzo[1,3]dioxole-5-carbaldehyde (14)

To compound **12** (0.2 g, 0.67 mmol) in 20 mL of THF at $-105\text{ }^{\circ}\text{C}$ was added *tert*-BuLi dropwise. The addition rate was about one drop per second. After ten minutes, anhydrous DMF (0.16 mL, 2 mmol) was added at $-105\text{ }^{\circ}\text{C}$. The mixture was stirred and warmed to $-20\text{ }^{\circ}\text{C}$ slowly. Aqueous 0.5M AcOH (4 mL) was added to quench the reaction. The solution was extracted with H_2O and ethyl acetate ($20\text{ mL} \times 2$), washed with brine, and dried with $MgSO_4$. Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 2:1) afforded product **14** (1.32 g, 74% yield). 1H NMR (300 MHz, $CDCl_3$) δ 2.69-2.77 (m, 2H), 3.51 & 4.05 (t, J = 9.0 Hz, 2H), 5.16-5.19 & 5.37-5.40 (m, 2H), 6.07-6.10 & 7.08-7.11 (m, 2H), 6.18 (s, 2H), 6.88 (d, J = 8.1 Hz, 1H), 7.00 (d, J = 8.1 Hz, 1H), 10.10 & 10.15 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.8 & 30.1, 45.4 & 47.7, 103.3, 112.7, 112.9, 117.0, 121.0, 121.8, 130.0, 130.6, 149.9 & 149.9, 164.5, 187.3. TLC (ethyl acetate: hexane = 1:1) R_f = 0.37.

4-[6-(2,3-Dihydropyrrole-1-carbonyl)-benzo[1,3]dioxol-5-yl]but-3-en-2-one (15)

Compound **14** (0.15 g, 0.6 mmol) and 1-triphenylphosphoranylidene-2-propanone (0.22 g, 0.7 mmol) were dissolved in 30 mL of benzene and heated to $80\text{ }^{\circ}\text{C}$ for 4 h. The mixture was cooled to room temperature. Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 1:2) afforded product **15** (0.16 g, 92% yield) as a white solid. 1H NMR (300 MHz, $CDCl_3$) δ 2.32 & 2.33 (s, 3H), 2.71-2.77 (m, 2H), 3.55

& 4.05 (t, $J = 7.2$ Hz, 2H), 5.18 & 5.41 (m, 1H), 6.11 & 6.12 (s, 2H), 6.85 (q, $J = 13.8$ Hz, $J = 7.8$ Hz, 2H), 7.01 (d, $J = 16.5$ Hz, 1H), 7.40 (d, $J = 16.5$ Hz, 1H). TLC (ethyl acetate: hexane = 1:2) $R_f = 0.22$.

{6-[3-(*tert*-Butyldimethylsilanyloxy)buta-1,3-dienyl]benzo[1,3]dioxol-5-yl}-(2,3-dihydropyrrol-1-yl)methanone (7)

Enone **15** (80 mg, 0.28 mmol) in 20 mL of THF at 0 °C was added Et₃N (113 mg, 1.12 mmol), followed by TBSOTf (0.22 g, 0.84 mmol). After 1 h at 0 °C, the solution was extracted with H₂O and ethyl acetate (20 mL × 2), washed with brine, and dried with MgSO₄. Evaporation of the solvent and purification by flash chromatography (hexane: ethyl acetate = 2:1) afforded product **7** (0.114 g, 95% yield) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 0.17 & 0.16 (s, 6H), 0.97 & 0.95 (s, 9H), 2.58 -2.71 (m, 2H), 3.99 & 3.49 (t, $J = 6.6$ Hz, 2H), 4.44 & 4.45 (d, $J = 8.1$ Hz, 2H), 5.10 & 5.31 (m, 1H), 6.05 (m, 1H), 6.06 (s, 2H), 6.64-6.74 (m, 2H), 6.79 (d, $J = 6$ Hz, 1H), 6.97 & 7.00 (d, $J = 8.7$ Hz, 1H). TLC (ethyl acetate: hexane = 1:2) $R_f = 0.73$.

2-(*tert*-Butyldimethylsilanyloxy)-3,3a,4,5,12b,12c-hexahydro-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-7-one (16) and 2-(*tert*-Butyldimethylsilanyloxy)-3,3a,4,5,12b,12c-hexahydro-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-7-one (6)

Compound **7** (30 mg, 0.075 mmol) in 8 mL of toluene in sealed tube was bubbled with argon for 5 minutes. The tube was sealed under argon atmosphere and heated to 190 °C for 4 hours. After the solution was cooled to room temperature, vacuum evaporation

removed solvent. The residue was purification by flash chromatography (hexane: ethyl acetate = 1:1) to afford **16** and **6** (21 mg, 70% yield) in 2:1 ratio.

(16): ^1H NMR (400 MHz, CDCl_3) δ 0.09 (s, 3H), 0.13 (s, 3H), 0.88 (s, 9H), 1.82 (dd, $J = 8.4$ Hz, $J = 6.8$ Hz, 1H), 1.90-1.98 (m, 1H), 2.06-2.12 (m, 1H), 2.18 (dd, $J = 17.2$ Hz, $J = 6.4$ Hz, 1H), 3.15 (s, 1H), 3.33 (m, 1H), 3.41 (m, 1H), 3.85 (dd, $J = 12$ Hz, $J = 7.2$ Hz, 1H), 3.95 (m, 1H), 4.71 (t, $J = 2.8$ Hz, 1H), 6.04 (dd, $J = 14.4$ Hz, $J = 3.2$ Hz), 6.78 (d, $J = 8$ Hz, 1H), 7.66 (d, $J = 8$ Hz, 1H).

(6): ^1H NMR (300 MHz, CDCl_3) δ 0.18 (s, 3H), 0.95 (s, 6H), 1.65 (m, 1H), 2.00 9m, 2H), 2.48 (m, 1H), 3.30 (m, 1H), 3.39 (m, 1H), 3.59 (m, 1H), 4.09-4.21 (m, 2H), 5.85 (t, $J = 2.7$ Hz, 1H), 6.10 (d, $J = 1.2$ Hz, 2H), 6.78 (d, $J = 8.4$ Hz, 1H), 7.65 (d, $J = 8.4$ Hz, 1H); MS m/z 399, 342, 268, 226, 219, 189; HRMS m/z for $\text{C}_{22}\text{H}_{29}\text{O}_4\text{NSi}$ calcd. 399.1866, measd. 399.1871. TLC (ethyl acetate: hexane = 2:1) $R_f = 0.18$.

1-Hydroxy-3,3a,4,5,12b,12c-hexahydro-1H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridine-2,7-dione (17)

To compound **16** and **6** (20 mg, 0.05 mmol) in 5 mL of CH_2Cl_2 at -78°C was added freshly prepared DMDO (about 0.063 M, 2 mL). The solution was warmed slowly to room temperature. The solvent was removed by vacuum evaporation and the residue was dissolved in 5 mL of CH_3CN , followed by TBAF·AcOH (1 M, 0.05 mL) addition at room temperature. The solution was stirred at room temperature for 1 hour. Evaporation of the solvent and purification by preparative TLC plate (ethyl acetate: methanol = 20:1) afforded compound **17** (13 mg, 65% yield) as a 3:1 mixture. ^1H NMR (400 MHz, CDCl_3) δ 1.92 (m, 1H), 2.48 (m, 1H), 2.67 (dd, $J = 14.4$ Hz, $J = 6.4$ Hz, 1H), 2.90 (m, 1H), 3.37 (m, 2H),

3.83 (m, 1H), 3.93 (m, 1H), 4.04 (m, 1H), 4.22-4.37 (m, 1H), 6.00 & 6.06 (d, $J = 1.6$ Hz, 1H), 6.14 & 6.12 (d, $J = 1.6$ Hz, 1H), 6.87 (d, $J = 8$ Hz, 1H), 7.76 & 7.69 (d, $J = 8$ Hz, 1H); MS m/z 301, 272, 229, 191, 69, 39; HRMS m/z for $C_{16}H_{15}O_5N$ calcd. 301.0950, measd. 301.0954. TLC (ethyl acetate: methanol = 9:1) $R_f = 0.23$.

2-(tert-Butyldimethylsilanyloxy)-4,5-dihydro-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-7-one (18)

To compound **16** and **6** (10 mg, 0.025 mmol) in 4 mL of toluene at room temperature was added DDQ (11.4 mg, 0.05 mmol). The mixture was stirred at rt for 24 hours, followed by aqueous saturated NaS_2O_3 solution to reduce the remained DDQ. The aqueous solution was extracted by ethyl acetate (20 mL). The organic layer was washed with saturated $NaHCO_3$, brine, and dried with $MgSO_4$. Separation by preparative TLC (CH_2Cl_2 : ethyl acetate = 20:1) to give compound **18** (1.8 mg, yield 18%, conversion 98%). 1H NMR (400 MHz, $CDCl_3$) δ 0.23 (s, 6H), 1.02 (s, 9H), 3.38 (t, $J = 8$ Hz, 2H), 4.45 (t, $J = 8$ Hz, 2H), 6.27 (s, 2H), 6.88 (d, $J = 2$ Hz, 1H), 7.08 (d, $J = 8.4$ Hz, 1H), 7.64 (d, $J = 2$ Hz, 1H), 8.16 (d, $J = 8.4$ Hz, 1H); MS m/z 395, 338, 280, 264, 169, 74, 54; HRMS m/z for $C_{22}H_{25}O_4NSi$ calcd. 395.1553, measd. 395.1558. TLC (ethyl acetate: hexane = 2:1) $R_f = 0.18$.

2-Hydroxy-4,5-dihydro-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-7-one (19)

To compound **18** (3 mg, 0.0076 mmol) in 6 mL of THF at 0 °C was added TBAF (1 M, 15 μ L). The mixture was stirred at 0 °C for 1h, neutralized by 0.5 M AcOH, and extracted with H_2O and ethyl acetate (5 mL \times 4). The organic layers were combined, washed with brine, and dried with $MgSO_4$. Separation by preparative TLC (hexane: ethyl acetate =

1:2) to give compound **19** (1.7 mg, yield 80%). ^1H NMR (400 MHz, CD_3COCD_3) δ 3.39 (t, $J = 8.4$ Hz, 2H), 4.34 (t, $J = 8.4$ Hz, 2H), 6.36 (s, 2H), 6.97 (d, $J = 1.6$ Hz, 1H), 7.15 (d, $J = 8$ Hz, 1H), 7.63 (d, $J = 1.6$ Hz, 1H), 8.05 (d, $J = 8$ Hz, 1H); MS m/z 281, 44; HRMS m/z for $\text{C}_{16}\text{H}_{11}\text{O}_4\text{N}$ calcd. 281.0688, measd. 281.0692. TLC (ethyl acetate: hexane = 2:1) $R_f = 0.125$.

Oxogalanthine lactam (2)

To compound **19** (1.7 mg, 0.007 mmol) in 2 mL of acetone was added K_2CO_3 (9.8 mg, 0.07 mmol). The mixture was cooled to 0°C and followed by the addition of MeI (10 μL , 0.07 mmol). The mixture was warmed to room temperature slowly and stirred at room temperature for 4 h. Evaporation removed most of the solvent. Separation by preparative TLC (hexane: ethyl acetate = 1:2) to give compound **2** (1.8 mg, yield 100%). ^1H NMR (400 MHz, CDCl_3) δ 3.41 (t, $J = 8$ Hz, 2H), 3.98 (s, 3H), 4.46 (t, $J = 8$ Hz, 2H), 6.28 (s, 2H), 6.98 (d, $J = 1.6$ Hz, 1H), 7.10 (d, $J = 8.4$ Hz, 1H), 7.68 (d, $J = 1.6$ Hz, 1H), 8.18 (d, $J = 8.4$ Hz, 1H); MS m/z 295, 280, 278; HRMS m/z for $\text{C}_{17}\text{H}_{13}\text{O}_4\text{N}$ calcd. 295.0845, measd. 295.0848. TLC (ethyl acetate: hexane = 2:1) $R_f = 0.24$.

2-(tert-Butyl-dimethyl-silanyloxy)-3,3a,4,5,12b,12c-hexahydro-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-7-one (16)

To compound **16** and **6** mixture (6 mg, 0.015 mmol) in 4 mL of THF at -78°C was added freshly prepared LiTMP (0.1 M, 0.18 mL, 0.018 mmol) slowly. The mixture was warmed to 0°C slowly, and quenched with 1 drop of AcOH in 2 mL of THF. The solution was extracted with H_2O and ethyl acetate (10 mL \times 2), washed with brine, and dried with MgSO_4 . Evaporation of solvent and purification by flash chromatography (hexane: ethyl

acetate = 2:1) afforded product **16** (3 mg, 50% yield). ^1H NMR (400 MHz, CDCl_3) δ 0.09 (s, 3H), 0.13 (s, 3H), 0.88 (s, 9H), 1.82 (dd, $J = 8.4$ Hz, $J = 6.8$ Hz, 1H), 1.90-1.98 (m, 1H), 2.06-2.12 (m, 1H), 2.18 (dd, $J = 17.2$ Hz, $J = 6.4$ Hz, 1H), 3.15 (s, 1H), 3.33 (m, 1H), 3.41 (m, 1H), 3.85 (dd, $J = 12$ Hz, $J = 7.2$ Hz, 1H), 3.95 (m, 1H), 4.71 (t, $J = 2.8$ Hz, 1H), 6.04 (dd, $J = 14.4$ Hz, $J = 3.2$ Hz), 6.78 (d, $J = 8$ Hz, 1H), 7.66 (d, $J = 8$ Hz, 1H); MS m/z 399, 342, 268, 226, 219, 189; HRMS m/z for $\text{C}_{22}\text{H}_{29}\text{O}_4\text{NSi}$ calcd. 399.1866, meads. 399.1871. TLC (ethyl acetate: hexane = 2:1) $R_f = 0.18$.

References:

1. Drosten, C.; Gunther, S.; Preiser, W.; van der Werf, S.; Brodt, H.R.; Becker, S.; Rabenau, H.; Panning, M.; Kolesnikova, L.; Fouchier, R. A.; Berger, A.; Burguiere, A. M.; Cinatl, J.; Eickmann, M.; Escriu, N.; Grywna, K.; Kramme, S.; Manuguerra, J. C.; Muller, S.; Rickerts, V.; Sturmer, M.; Vieth, S.; Klenk, H. D.; Osterhaus, A. D.; Schmitz, H.; Doerr, H. W. *N. Engl. J. Med.* **2003**, *348*, 1967-1976.
2. Ksiazek, T. G.; Erdman, D.; Goldsmith, C. S.; Zaki, S. R.; Peret, T.; Emery, S.; Tong, S.; Urbani, C.; Comer, J. A.; Lim, W.; Rollin, P. E.; Dowell, S. F.; Ling, A. E.; Humphrey, C. D.; Shieh, W. J.; Guarner, J.; Paddock, C. D.; Rota, P.; Fields, B.; DeRisi, J.; Yang, J. Y.; Cox, N.; Hughes, J. M.; LeDuc, J. W.; Bellini, W. J.; Anderson, L. J. *N. Engl. J. Med.* **2003**, *348*, 1953-1966.
3. Zeng, F. Y.; Chan, C. W.; Chan, M. N.; Chen, J. D.; Chow, K. Y.; Hon, C. C.; Hui, K. H.; Li, J.; Li, V. Y.; Wang, C. Y.; Wang, P. Y.; Guan, Y.; Zheng, B.; Poon, L. L.;

- Chan, K. H.; Yuen, K. Y.; Peiris, J. S.; Leung, F. C. *Exp. Biol. Med.* **2003**, *228*, 866-873.
4. Li, S. Y.; Chen, C.; Zhang, H. Q.; Guo, H. Y.; Wang, H.; Wang, L.; Zhang, X.; Hua, S. N.; Yu, J.; Xiao, P. G.; Li, R. S.; Tan, X. H. *Antiviral Research* , **2005**, *67*, 18-23
 5. Hoshino, O. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, **1998**, *51*, 323-424.
 6. (a) Fales, H. M.; Warnhoff, E. W.; Wildman, W. C. *J. Amer. Chem. Soc.* **1955**, *77*, 5885-5890. (b) Ji, X., Melman, N.; Jacobson, K. A. *J. Med. Chem.* **1996**, *39*, 781-788
 7. Evidente, A.; Andolfi, Anna.; Abou-Donia, A. H.; Touema, S. M.; Hammada, H. M.; Shawky, E.; Motta, A. *Phytochemistry* , **2004**, *65*, 2113-2118.
 8. Ganem, B. *Tetrahedron Lett.* **1971**, *44*, 4105-4108.
 9. (a) Irie, H.; Nishitani, Y.; Sigita, M.; Uyeo, S. *J. Chem. Soc. Chem. Commun.*, **1970**, 1313-1315. (b) Irie, H.; Nagai, Y.; Tamoto, K.; Tanaka, H. *J. Chem. Soc. Chem. Commun.*, **1973**, 302. (c) Tsuda, Y.; Sano, T.; Taga, J.; Isobe, K.; Toda, J.; Irie, H.; Tanka, H.; Takagi, S.; Yamaki, M.; Murata, M. *J. Chem. Soc. Chem. Commun.*, **1975**, 933. (d) Sano, T.; Kashiwaba, N.; Toda, J.; Tsuda, Y.; Irie, H. *Heterocycles*, **1980**, *14*, 1097.
 10. Møller, O.; Steinberg, E. M.; Torssell, K. *Acta. Chem. Scand. Sect. B*, **1978**, *32*, 98.
 11. (a) Umezawa, B.; Hoshino, O.; Sawaki, S.; Sashida, H.; Mori, K. *Heterocycles*, **1979**, *12*, 1475. (b) Umezawa, B.; Hoshino, O.; Sawaki, S.; Sashida, H.; Mori, K.; Hamada, Y.; Kotera, K.; Iitaka, Y. *Tetrahedron*, **1984**, *40*, 1783. (c) Ishizaki, M.; Kai, Y.;

- Hoshino, O. *ACH-Models in Chem.* **1998**, *135*, 529-552. (d) Ishizaki, M.; Kai, Y.; Hoshino, O. *Heterocycles*, **2002**, *57*, 2279-2297.
12. (a) Martin, S. F.; Tu, C. *J. Org. Chem.* **1981**, *46*, 3763. (b) Martin, S. F.; Tu, C.; Kimura, M.; Simonsen, S. H. *J. Org. Chem.* **1981**, *47*, 3634.
13. Boeckman, R. K. Jr.; Goldstein, S. W.; Walters, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 8250.
14. Stephenson, G. R.; Palotai, I. M.; Ross, W. J.; Tupper, D. E. *Synlett.* **1991**, 586-588.
15. Tsuda, Y.; Sano, T.; Taga, J.; Isobe, K.; Toda, J.; Takagi, S.; Yamaki, M.; Murata, M.; Irie, H.; Tannaka, H. *J. Chem. Soc. Perkin. Trans. 1*, **1979**, 1358-1363.
16. Hoshino, O.; Ishizaki, M.; Kamei, K.; Taguchi, M.; Nagao, T.; Iwaoka, K.; Sawaki, S.; Umezawa, B.; Iitaka, Y. *J. Chem. Soc. Perkin. Trans. 1*, **1996**, 571-580.
17. Schultz, A. G.; Holoboski, M. A.; Smyth, M. S. *J. Am. Chem. Soc.* **1996**, *118*, 6210-6219.
18. Lauk, U.; Durst, D.; Fischer, W. *Tetrahedron Lett.* **1991**, *32*, 65-68.
19. Normatov, M.; Abduazimov, Kh. A.; Yunusov, S. Y. *Uzb. Khim. Zh.* **1965**, *9*, 25. *CA*, **1965**, *63*, 7061.
20. Kraus, G. A.; Neuenschwander, K. *J. Org. Chem.* **1981**, *46*, 4791-4792.
21. Padwa, A.; Dimitroff, M.; Waterson, G. A.; Wu, T. *J. Org. Chem.* **1998**, *63*, 3986-3997.
22. Nomura, Y.; Ogawa, K.; Takeuchi, Y.; Tomoda, S. *Chem. Lett.* **1977**, 693-696.
23. Perez, D.; Bures, G.; Guitian, E.; Castedo, L. *J. Org. Chem.* **1996**, *61*, 1650-1654.

GENERAL CONCLUSIONS

In this dissertation, the synthesis of natural products and their analogs related to *Echinacea* and *Hypericum* (St. John's wort) have been investigated. During the process, novel synthetic methodologies have been developed.

Chapter 1 describes the direct synthesis of Hyperolactone C in two steps from known compounds. The key transformation is a tandem Claisen rearrangement and lactonization. Hyperolactone A and B could be achieved by the same strategy. Hyperolactone C could be the precursor for the synthesis of biyouyanagin A.

Chapter 2 describes regioselective Diels-Alder reaction directed by remote substituents. 5-Methoxysubstituted 1,4-phenanthrenequinones exhibit remarkable regioselectivity in Diels-Alder reactions. 5-Formylsubstituted 1,4-naphthoquinone also exhibits high regioselectivity in Diels-Alder reactions. The selectivity is explained by molecular electrostatic potential (MEP) calculations. The selectivity directed by remote substituents has useful applications in natural products synthesis.

Chapter 3 describes the synthesis of phytochemical medicinal reagents, pterocarpins, based on benzofuran and quinone coupling. The use of quinone monoketal extends the range of quinols that can be produced by carbanion reactions. The stereochemistry is easily controlled by Pd/C hydrogenation.

Chapter 4 describes a general synthesis of three classes of natural products, flavones, aurones, and acyl phloroglucinols, from one type of intermediate α 1,3-benzodioxin-4-one. Regiochemistry at C-3 and C-8 of flavone compounds have been studied, which has been applied to the synthesis of flavopyridol analogs.

Chapter 5 describes a study toward the total synthesis of an anti-SARS drug candidate, lycorine, and other lycorine-type alkaloids. The pentacyclic lycorine skeleton has been constructed by an intramolecular Diels-Alder reaction. A facile *N*-acyl-2-pyrroline synthesis has been applied to prepare the dienophile. The lycorine intermediate would be applied to the total synthesis of amarbellisine and other lycorine-type alkaloids.

ACKNOWLEDGMENTS

First, I would like to express my sincere gratitude to Dr. George A. Kraus, my major professor, for his guidance, support, and encouragement. Without his patience and advice, this thesis would not have been possible.

I would like to thank Dr. Richard C. Larock, Dr. Yan Zhao, Dr. Robert S. Houk, and Dr. Gary D. Osweiler for serving on my program of study committee.

I would also like to thank the past and present Kraus group members for their helpful discussion and unforgettable friendships, which will remain in my memory. I am grateful to all the friends at Iowa State through my graduate studies, particularly the colleagues in Chemistry Department. They helped make my graduate study at Iowa State an enjoyable and positive experience.

My heartfelt appreciation and love go to my parents for their love, support, and sacrifices. My mother's encouragement has been very important. My father has been a valuable role model in my life, demonstrating persistence, patience, and hard work. This thesis is dedicated to them.